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(54) **SULFONATED AMINO ACID DERIVATIVES AND METALLOPROTEINASE INHIBITORS  
CONTAINING THE SAME**

SULFONIERTE AMINOSÄUREDERIVATE UND METALLOPROTEINASE-INHIBITOREN, DIE DIESE  
ENTHALTEN

DERIVES D'ACIDES AMINES SULFONES ET INHIBITEURS DE METALLOPROTEINASES  
CONTENANT CES DERIVES

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**Description****Technical Field**

5 [0001] This application relates to sulfonated amino acid derivatives and metalloproteinase inhibitors containing the same.

**Background Art**

10 [0002] An extracellular matrix consists of collagen or proteoglycan has a function to support tissues, and plays a role in a maintaining of a cell functions, for example propagation, differentiation or adhesion. Matrix metalloproteinases (MMP) such as gelatinase, stromelysin or collagenase have an important role in degradation of an extracellular matrix, and these enzymes work for growth or tissue remodeling under physiological conditions. Therefore, it is considered that these enzymes participate in progression of various kind of diseases involving breakdown and fibrosis of tissues, such as osteoarthritis, rheumatoid arthritis, corneal ulceration, perindontitis, metastasis and invasion of tumor, and virus infection (for example, HIV infection). At the present time, it is not clear which enzyme participates in the above diseases seriously, but it is considered that these enzymes at least participate in tissue breakdown. As metalloproteinase inhibitors of amino acid derivatives, for example hydroxamic acid derivatives of amino acids (JP-A-6-2562939), carboxylic acid derivatives of amino acids and/or their hydroxamic acid derivatives (WO95/35276) are disclosed

20 [0003] WO 96/00214 discloses arylsulfonamido-substituted hydroxamic acids as MMP-inhibitors.

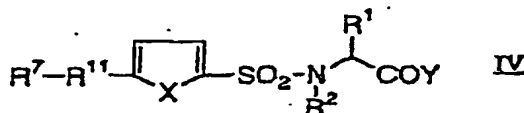
**Disclosure of the Invention.**

25 [0004] If it is able to inhibit the activity of MMP, it is considered that MMP inhibitors contribute to an improvement and prevention of the above diseases caused by or related to its activity. Therefore, development of MMP inhibitors has long been desired.

[0005] In the above situation, the inventors of the present invention found that a kind of sulfonamide derivatives have strong activity to inhibit MMP

30 [0006] The present invention relates to a composition for inhibiting metalloproteinase which contains a compound of the formula IV, VIII or XIII. b) A composition for inhibiting metalloproteinase as mentioned above, which is a composition for inhibiting type-IV collagenase.

1) A compound of the formula IV:



wherein R<sup>1</sup> is

optionally substituted C1-C6 straight or branched alkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, amino, methylamino, dimethylamino, carbamoylamino, guanidino, phenyl, or benzyloxy,

45 optionally substituted aryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino,

alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

50 optionally substituted aralkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

55 optionally substituted heteroaryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano,

haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido, or

optionally substituted heteroarylalkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

R<sup>2</sup> is

hydrogen atom,

optionally substituted C1-C6 straight or branched alkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, amino, methylamino, dimethylamino, carbamoylamino, guanidino, phenyl, or benzyloxy,

optionally substituted aryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

optionally substituted aralkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

optionally substituted heteroaryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

or

optionally substituted heteroarylalkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

R<sup>7</sup> is

optionally substituted aryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureide or phenylureido,

or

optionally substituted heteroaryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido;

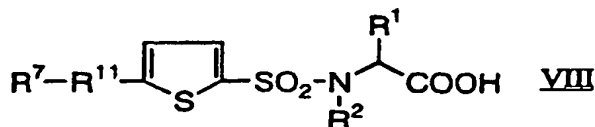
R<sup>11</sup> is -CH=CH-, or -C≡C-;

X is oxygen atom or sulfur atom;

Y is -NHOH or -OH,

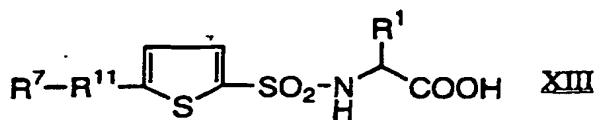
its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

2) A compound of the formula VIII:



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>7</sup>, and R<sup>11</sup> are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

3) A compound of the formula XIII:



wherein R<sup>1</sup>, R<sup>7</sup>, and R<sup>11</sup> are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

[0007] C) The compound of anyone of above 1) to 3) wherein a configuration of asymmetric carbon atoms bonding with R<sup>1</sup> is R configuration Further, this invention relates to a pharmaceutical composition, a composition for inhibiting metalloproteinase, and a composition for inhibiting type IV collagenase which contain the compound above 1) to 3) and C).

[0008] All of compounds of above 1) to 3) and C) have strong metalloproteinase inhibitory activity, and the following compound is more preferable:

1) A compound of above 1) to 3), wherein R<sup>7</sup> is phenyl optionally substituted with one or more substituents selected from the group consisting of alkoxy, alkylthio, and alkyl.

[0009] The term "alkyl" herein used means C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, i-pentyl, neo-pentyl or tert-pentyl.

[0010] The term "lower alkyl" herein used means C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl or tert-butyl.

[0011] The term "C<sub>3</sub>-C<sub>8</sub> cycloalkyl" herein used is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

[0012] The term "aryl" herein used means monocyclic or condensed ring aromatic hydrocarbons. Examples of the aryl are phenyl or naphthyl.

[0013] The term "aralkyl" herein used means the above mentioned alkyl substituted by the above mentioned aryl at any possible position. Examples of the aralkyl are benzyl, phenethyl, phenylpropyl (e.g., 3-phenylpropyl), naphthylmethyl (a-naphthylmethyl) or anthrylmethyl (9-anthrylmethyl). Benzyl is preferred. The aryl part may optionally be substituted.

[0014] The term "heteroaryl" herein used means a 5 to 6 membered aromatic heterocyclic group which contains one or more hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in the ring and may be fused with a carbocyclic ring or other heterocyclic ring at any possible position. Examples of the heteroaryl are pyrrolyl (e.g., 1-pyrrolyl), indolyl (e.g., 2-indolyl), carbazolyl (e.g., 3-carbazolyl), imidazolyl (e.g., 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl), benzimidazolyl (e.g., 2-benzimidazolyl), indazolyl (e.g., 3-indazolyl), indolizynyl (e.g., 6-indolizynyl), pyridyl (e.g., 4-pyridyl), quinolyl (e.g., 5-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), acridinyl (e.g., 1-acridinyl), phenanthridinyl (e.g., 2-phenanthridinyl), pyridazinyl (e.g., 3-pyridazinyl), pyrimidinyl (e.g., 4-pyrimidinyl), pyrazinyl (e.g., 2-pyrazinyl), cinnolinyl (e.g., 3-cinnolinyl), phthalazinyl (e.g., 2-phthalazinyl), quinazolinyl (e.g., 2-quinazolinyl), isoxazolyl (e.g., 3-isoxazolyl), benzisoxazolyl (e.g., 3-benzisoxazolyl), oxazolyl (e.g., 2-oxazolyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzoxadiazolyl (e.g., 4-benzoxadiazolyl), isothiazolyl (e.g., 3-isothiazolyl), benzisothiazolyl (e.g., 2-benzisothiazolyl), thiazolyl (e.g., 2-thiazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), furyl (e.g., 3-furyl), benzofuryl (e.g., 3-benzofuryl), thienyl (e.g., 2-thienyl), benzothieryl (e.g., 2-benzothieryl) or tetrazolyl. The aryl part of the above heteroaryl is optionally substituted.

[0015] The term "heteroarylalkyl" herein used means the above mentioned alkyl substituted with the above mentioned heteroaryl at any possible position. Examples of the heteroarylalkyl are thiazolylmethyl (e.g., 4-thiazolylmethyl), thiazolylethyl (e.g., 5-thiazolyl-2-ethyl), indolylmethyl (e.g., 2-indolylmethyl), imidazolylmethyl (e.g., 4-imidazolylmethyl), benzothiazolylmethyl (e.g., 2-benzothiazolylmethyl), benzopyrazolylmethyl (e.g., 1-benzopyrazolylmethyl), benzotriazolylmethyl (e.g., 4-benzotriazolylmethyl), benzoquinolylmethyl (e.g., 2-benzoquinolylmethyl), benzimidazolylmethyl (e.g., 2-benzimidazolylmethyl) or pyridylmethyl (e.g., 2-pyridylmethyl). The aryl part of the above heteroaryl is optionally substituted.

[0016] The term "arylene" herein used is exemplified by phenylene or naphthylene. Mentioned in more detail, it is exemplified by 1,2-phenylene, 1,3-phenylene or 1,4-phenylene.

[0017] The term "heteroarylene" herein used is exemplified by thiophen-diyl, furan-diyl or pyridin-diyl, in more detail, by 2,5-thiophen-diyl or 2,5-furan-diyl.

[0018] The term "non-aromatic heterocyclic group" herein used means 5 to 6 membered non-aromatic heterocyclic group which contains one or more hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in the ring, and may bind at any possible position. Examples of the non-aromatic heterocyclic group are morpholino, piperidino or pyrrolidino.

[0019] The term "alkoxy" herein used means alkoxy of which alkyl part is the above mentioned alkyl. Examples of the alkoxy are methoxy, ethoxy, propoxy, butoxy or pentyloxy.

[0020] The term "lower alkoxy" herein used means alkoxy of which alkyl part is the above mentioned lower alkyl. Examples of the lower alkoxy are methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy or tert-butoxy.

[0021] The term "halogen" herein used means fluoro, chloro, bromo, and iodo.

[0022] The term "alkylthio" herein used means alkylthio whose alkyl part is the above mentioned lower alkyl. Examples of the alkylthio are methylthio or ethylthio.

[0023] Substituents for "optionally substituted alkyl", "optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl", and "optionally substituted non-aromatic heterocyclic group" are hydroxy, alkoxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl), halogen (e.g., fluoro, chloro, bromo, and iodo), carboxy, alkoxy-carbonyl (e.g., methoxycarbonyl and ethoxycarbonyl), nitro, cyano, haloalkyl (e.g., trifluoromethyl), aryloxy (e.g., phenyloxy), substituted or unsubstituted amino (e.g., methylamino, dimethylamino, and carbamoylamino), guanidino, phenyl or benzyloxy. These substituents are able to bind them at one or more of any possible positions.

[0024] Substituents for the aromatic ring of "optionally substituted aryl", "optionally substituted aralkyl", "optionally substituted heteroaryl", "optionally substituted heteroarylalkyl", "optionally substituted arylene", and "optionally substituted heteroarylene" are, for example, hydroxy, alkoxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl), halogen (e.g., fluoro, chloro, bromo, and iodo), carboxy, alkoxy-carbonyl (e.g., methoxycarbonyl and ethoxycarbonyl), nitro, cyano, haloalkyl (e.g., trifluoromethyl), aryloxy (e.g., phenyloxy), substituted or unsubstituted amino (e.g., methylamino, dimethylamino, diethylamino, and benzylidenamino), guanidino, alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, i-pentyl, neo-pentyl, and tert-pentyl), alkenyl (e.g., vinyl and propenyl), alkynyl (e.g., ethynyl and phenylethynyl), alkanoyl (e.g., formyl, acetyl, and propionyl), acyloxy (e.g., acetyloxy), acylamino, alkylsulfonyl (e.g., methylsulfonyl), phenyl, benzyl, an azo group (e.g., phenylazo), optionally substituted heteroaryl (e.g., 3-pyridyl) or optionally substituted ureido (e.g., ureido and phenylureido). These substituents are able to bind to it at one more of any possible position.

#### Best Mode for Carrying Out the Invention

[0025] Compounds (Ia) and (Ib) are able to be synthesised from the corresponding  $\alpha$ -amino acids represented by the formula (XV) by means of the following 6 synthetic methods. Generally, it is possible of the invention by means of the method A. Each classified type of the compounds is possible to be produced by means of the methods B to F. However, these methods are only examples to produce the compounds represented by the formula IV, VIII and XIII. A compound represented by the formula IV, VIII or XIII produced by any other method is included in this invention.

[0026] Method A: A general synthetic method of the compound represented by the formula I.

[0027] Method B: A synthetic method of the compound wherein R<sup>3</sup> is optionally substituted arylene or optionally substituted heteroarylene, R<sup>4</sup> is -C $\equiv$ C-, and R<sup>5</sup> is optionally substituted aryl or optionally substituted heteroaryl.

[0028] Method C: A synthetic method of the compound wherein R<sup>3</sup> is optionally substituted arylene or optionally substituted heteroarylene, R<sup>4</sup> is a bond, and R<sup>5</sup> is optionally substituted aryl or optionally substituted heteroaryl.

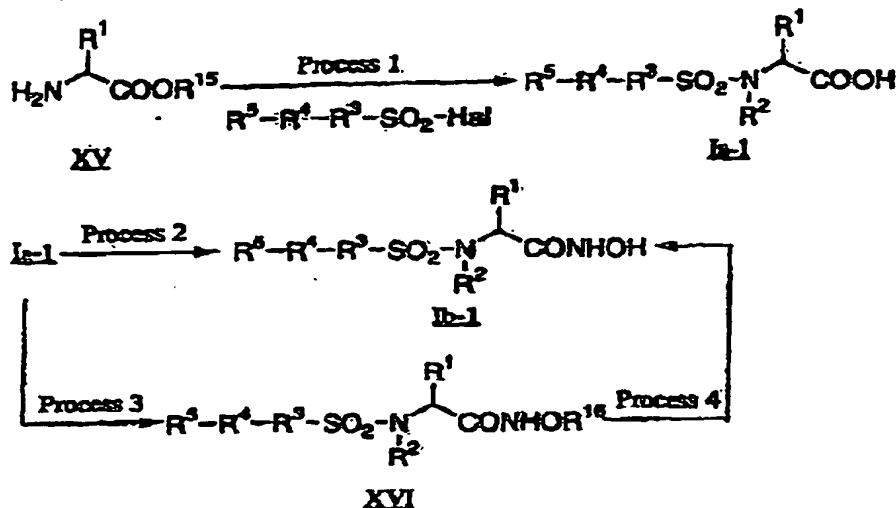
[0029] Method D: A synthetic method of the compound wherein R<sup>3</sup> is optionally substituted arylene or optionally substituted heteroarylene, R<sup>4</sup> is -CO-NH-, and R<sup>5</sup> is optionally substituted aryl or optionally substituted heteroaryl.

[0030] Method E: A synthetic method of the compound wherein R<sup>3</sup> is optionally substituted arylene or optionally substituted heteroarylene, R<sup>4</sup> is tetrazol-diyl, and R<sup>5</sup> is optionally substituted aryl or optionally substituted heteroaryl.

[0031] Method F: A synthetic method of the compound wherein R<sup>3</sup> is optionally substituted arylene or optionally substituted heteroarylene, R<sup>4</sup> is -CH=CH-, and R<sup>5</sup> is optionally substituted aryl or optionally substituted heteroaryl.

[0032] Details of these methods are explained as follows.

## (Method A)



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are as defined above, R<sup>15</sup> is hydrogen or a carboxy protective group. R<sup>16</sup> is a hydroxy protective group and Hal is halogen.

[0033] Convention of compound (XV) to compound (Ia-1) is sulfonation of an amino group of the compound (XV) (process 1). If necessary, after this reaction, N-alkylation, deprotection of a carboxyl protective group are carried out. Conversion of compound (Ia-1) to compound (Ib-1) is to obtain hydroxamic acid derivatives from carboxylic acid derivatives (process 2). To obtain compound (Ib-1) from compound (Ia-1), compound (Ia-1) may also be reacted with hydroxylamine having a hydroxyl protective group or its acidic salts to give compound (XVI) (process 3), followed by a deprotection (process 4). Conversion to sulfonyl derivatives and hydroxamic acid derivatives are able to be carried out according to an usual method. For example, an amino acid represented by the formula (XV) is reacted with a sulfonating agent such as sulfonyl halide represented by R<sup>5</sup>-R<sup>4</sup>-R<sup>3</sup>-SO<sub>2</sub>Hal (R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are as defined above; and Hal is halogen) and then hydroxylamine. Each process will hereinafter be described in more detail.

## (Process 1)

[0034] Some of amino acids represented by the formula (XV) or its acidic salts (e.g., hydrochloride, p-toluenesulfonate, and trifluoroacetate) which are starting materials are commercially available. The others are able to be synthesized in accordance with a method described in Zikkenkagakukoza, vol. 22, IV (nitrokagakukai). J. Med. Chem. 38, 1689-1700, 1995. Gary M. Keander et. al., some sulfonating agents are commercially available and the others are synthesized in accordance with a method described in Shin-zikkenkagakukoza, vol. 14, 1787, 1978, Synthesis 852-854, 1986. A carboxyl protective group is exemplified by esters (e.g., methyl ester, tert-butyl ester and benzyl ester). Deprotection of this protective group may be carried out by hydrolysis with acid (e.g., hydrochloride and trifluoroacetic acid) or base (e.g., sodium hydroxide) depending on the type of the group, or by catalytic reduction, e.g., under 10% palladium-carbon catalyst condition. To obtain a compound (Ib-1), the esters may directly be converted to hydroxamic acid by the method of process 2. When a compound (XV) is an amino acid wherein R<sup>15</sup> is hydrogen, preferable solvents for this sulfonylation are dimethylformamide tetrahydrofuran, dioxane, dimethylsulfoxide, acetonitrile, water, or mixed solvents thereof. When a compound (XV) is an amino acid wherein R<sup>15</sup> is a protective group such as an ester, a solvent for this sulfonylation is exemplified by the above solvents and mixed solvents of water-insoluble solvents (e.g., benzene and dichloromethane) and the above solvents. A base to be used in this sulfonylation is exemplified by organic bases such as triethylamine or N-methylmorpholine and inorganic bases such as sodium hydroxide, potassium hydroxide or potassium carbonate. Usually this reaction can be carried out at ice-cooling to room temperature. When R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, or R<sup>15</sup> of compound (Ia-1) contains a functional group(s) possibly interfering with this sulfonylation (e.g., hydroxy, mercapto, amino, and guanidino), it can previously be protected in accordance with a method described in "Protective Groups in Organic Synthesis" (Theodora W. Green (John Wiley & Sons)) and then deprotected at an appropriate step. When R<sup>2</sup> is not hydrogen, compound (Ia-1) wherein R<sup>2</sup> is hydrogen is further reacted with haloalkyl (e.g., methyl iodide, and ethyl iodide) or haloaralkyl (e.g., benzyl chloride, and benzyl bromide) in dimethylformamide, tetrahydrofuran or dioxane at a temperature range of ice-cooling to 80 °C, preferably ice-cooling to room temperature, for 3-10 hours, preferably 10-20

hours to give the desired N-R<sup>2</sup> derivative.

(Process 2)

**[0035]** A hydroxylamine is reacted with compound (Ia-1) or its reactive derivatives to give hydroxamic acid derivatives (Ib-1). A hydroxylamine is usually used as its acidic salts (e.g., hydrochloride, and phosphate, sulfate: commercially available) in the presence of a base. A base to be used in this reaction is exemplified by organic bases such as triethylamine, N, N-dimethylaniline or N-methylmorpholine and inorganic bases such as sodium hydroxide, potassium hydroxide or potassium carbonate. When compound (Ia-1) is used as a starting material of conversion to hydroxamic acid, this reaction is carried out in the presence of a peptide condensing agent (e.g., dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, N,N'-carbonyldiimidazole, or a mixture of one of the above agents with 1-hydroxybenzotriazole or N-hydroxy succinimide). A solvent for this reaction may be dimethylformamide, tetrahydrofuran, dioxane, dimethylsulfoxide, acetonitrile, water, and mixed solvents thereof. This reaction is carried out at -20°C to 40°C, preferably ice-cooling to room temperature, for 1 to 16 hours.

**[0036]** Acid anhydrides (especially, mixed acid anhydrides), acid halides, acid azides, and esters can be utilized in this reaction as a reactive derivative of compound (Ia-1). These reactive derivatives are produced by usual methods. For example, the acid anhydride derivatives can be produced by a reaction of compound (Ia-1) with acid halide derivatives (e.g., ethyl chlorocarbonate) in the presence of a base (e.g., triethylamine), and acid halide derivatives can be produced by a reaction of compound (Ia-1) with a halogenation agent (e.g., oxalylchloride, and thionylchloride). Ester derivatives may be inactive or active. Sulfonyl derivatives converted from a compound (XV) wherein R<sup>15</sup> is a carboxyl protective group (e.g., methyl, tert-butyl, and benzyl) at process 1 can be used as inactive esters without deprotection. Active esters can be produced by a reaction of compound (Ia-1), carbodiimide reagents (e.g., dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide), and hydroxy derivatives corresponding to the active ester residue such as 1-hydroxybenzotriazole or N-hydroxysuccinimide. A reaction condition of conversion of the reactive derivatives of compound (Ia-1) to hydroxamic acid may be the same as that of conversion of compound (Ia-1) itself to hydroxamic acid. The reactions of processes 1 and 2 are able to continuously be carried out in one-pot reaction.

(Process 3)

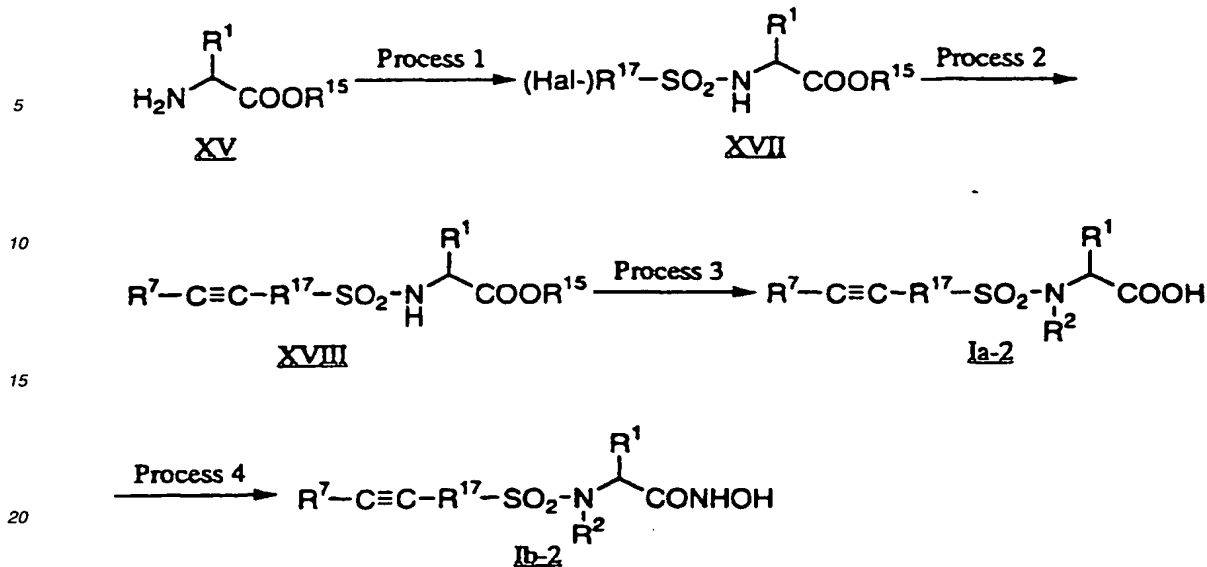
**[0037]** A protected hydroxylamine to be used in this reaction includes O-benzylhydroxylamine, O-(p-methoxybenzyl)hydroxylamine or O-(tert-butyl)hydroxylamine. This reaction condition may be in the same manner as that of process 2.

(Process 4)

**[0038]** This process for deprotection is carried out by catalytic reduction, treatment with conc. hydrochloric acid, or treatment with trifluoroacetic acid to give the desired compound (Ib-1). The compounds of this invention (Ia-1) and (Ib-1) can be isolated and purified by usual separation methods and purification methods (e.g., chromatography, or crystallization).

## (Method B)





wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>7</sup>, R<sup>15</sup>, and Hal are as defined above, R<sup>17</sup> is optionally substituted aryl or optionally substituted heteroaryl.

**[0039]** Conversion of compound (XV) to compound (XVII) is performed by sulfonation of an amino group of compound (XV) (process 1) in the same manner as that described in process 1 of method A. Conversion of compound (XVII) to compound (XVIII) is performed by Heck reaction (K. Sonogashira, Y. Tohda, and N. Hagihara, Tetrahedron Lett., 4467 (1975)) wherein halogen of R<sup>17</sup> is utilized to insert a triple bond (process 2). Conversion of compound (XVIII) to compound (Ia-2) is N-alkylation, deprotection of a carboxyl protective group (process 3), which can be carried out in the same manner as that described in process 1 of method A. Conversion of compound (Ia-2) to compound (Ib-2) is that of carboxylic acid derivatives to hydroxamic acid derivatives (process 4), which can be carried out in the same manner as those described in processes 2 to 4 of method A. Each process will hereinafter be described in more detail.

(Process 1)

**[0040]** This process may be carried out in the same manner as that described in process 1 of method A.

(Process 2)

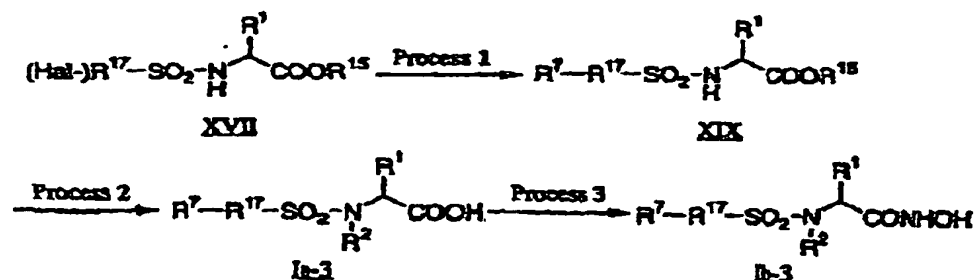
**[0041]** Compound (XVII) is reacted with optionally substituted aryl or optionally substituted heteroaryl having an ethynyl group such as ethynylbenzene in a solvent such as dimethylformamide, toluene, xylene, benzene or tetrahydrofuran in the presence of a palladium catalyst (e.g., Pd(Ph<sub>3</sub>P)<sub>3</sub>Cl<sub>2</sub>), a divalent copper reagent (e.g., CuI), and an organic base (e.g., triethylamine, and diisopropylethylamine) to give a desired compound (XVIII) (Heck reaction). This reaction is carried out at room temperature to 100 °C, preferably room temperature to 80 °C. This reaction is completed for 3 to 30 hours, preferably 10 to 20 hours. When optionally substituted aryl or optionally substituted heteroaryl has a substituent (s) interfering with this reaction, the substituent(s) can previously be protected in accordance with a method of "Protective Groups in Organic Synthesis" (Theodora W. Green (John Wiley & Sons)), and then deprotected at an appropriate step.

(Process 3)

**[0042]** This process may be carried out in the same manner as that described in process 1 of method A.

(Process 4)

**[0043]** This process may be carried out in the same manner as those described in processes 2 to 4 of method A.

**(Method C)**

wherein  $\text{R}^3$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^{15}$ ,  $\text{R}^{17}$ , and Hal are as defined above.

[0044] Conversion of compound (XVII) to compound (XIX) is performed by Suzuki reaction (M. J. Sharp and V. Shieckus, Tetrahedron Lett., 28, 5997 (1985)) wherein halogen of  $\text{R}^{17}$  is utilized to introduce aryl or heteroaryl (process 1). Conversion of compound (XIX) to compound (Ia-3) is N-alkylation, deprotection of a carboxyl protective group (process 2) and this process can be carried out in the same manner as that described in process 1 of method A. Conversion of compound (Ia-3) to compound (Ib-3) is that of carboxylic acid derivatives to hydroxamic acid derivatives (process 3), and this process can be carried out in the same manner as those described in processes 2 to 4 of method A. Each process will hereinafter be described in more detail.

(process 1)

[0045] Compound (XVII) is reacted with optionally substituted aryl or optionally substituted heteroaryl having a  $\text{B}(\text{OH})_2$  (otherwise  $\text{B}(\text{Et})_2$ ) group such as phenylboronic acid in a solvent such as dimethylformamide, toluene, xylene, benzene, tetrahydrofuran etc. in the presence of a palladium catalyst (e.g.,  $\text{Pd}(\text{Ph}_3\text{P})_4$ ) and a base (e.g., potassium carbonate, calcium carbonate, triethylamine or sodium methoxide) to give the desired compound (XIX) (Suzuki reaction). This reaction is carried out at room temperature to 100 °C, preferably room temperature to 80 °C. This reaction is completed for 5 to 50 hours, preferably 15 to 30 hours. When optionally substituted aryl or optionally substituted heteroaryl has a substituent(s) interfering with this reaction, the substituent(s) can previously be protected in accordance with a method of "Protective Groups in Organic Synthesis" (Theodora W. Green (John Wiley & Sons)) and then deprotected at an appropriate step.

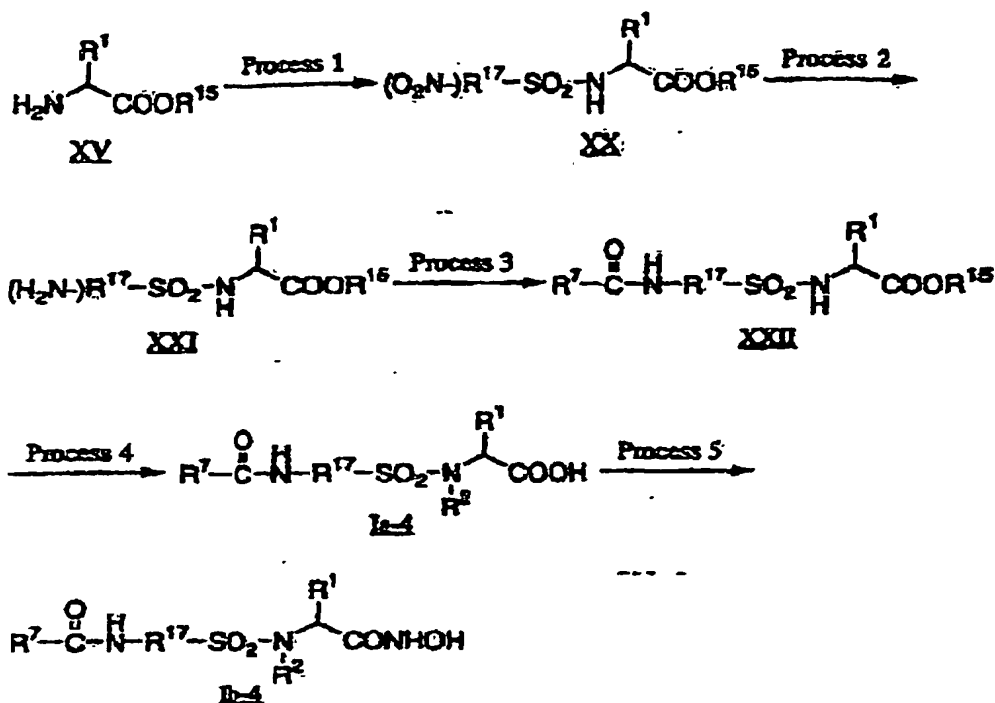
(Process 2)

[0046] This process may be carried out in the same manner as that described in process 1 of method A.

(Process 3)

[0047] This process may be carried out in the same manner as those described in processes 2 to 4 of method A.

**(Method D)**



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>7</sup>, R<sup>15</sup>, R<sup>17</sup>, and Hal are as defined above.

[0048] Conversion of compound (XV) to compound (XX) is sulfonation of an amino group of the compound (XV) (process 1) and this process may be carried out in the same manner as that described in process 1 of method A. Conversion of compound (XX) to compound (XXI) is reduction of a nitro group of R<sup>17</sup> to an amino group (process 2) and this process can be carried out by catalytic reduction or other reduction using hydrochloric chloride - Fe or hydrochloric chloride - Sn. Conversion of compound (XXI) to compound (XXII) is performed by usual amide bond formation reaction wherein an amino group of R<sup>17</sup> is utilized (process 3). Conversion of compound (XXII) to compound (Ia-4) is N-alkylation, deprotection of a carboxyl protective group (process 4) of compound (XXII) and this process can be carried out in the same manner as that described in process 1 of method A. Conversion of compound (Ia-4) to compound (Ib-4) is that of carboxylic acid derivatives to hydroxamic acid derivatives (process 5) and this process can be carried out in the same manner as those described in processes 2 to 4 of method A. Each process will hereinafter be described in more detail.

(process 1)

[0049] This process may be carried out in the same manner as that described in process 1 or method A.

(Process 2)

[0050] Compound (XX) is treated with hydrogen in a solvent such as methanol, ethanol, ethyl acetate or acetic acid in the presence of a catalyst (e.g. Pd-C, PtO<sub>2</sub> or Raney Ni), under a no-pressure or pressured condition to give the desired compound (XXI). This reaction is carried out at a temperature under ice-cooling to 80 °C, preferably room temperature to 50 °C, and is completed for 1 to 10 hours, preferably 2 to 5 hours.

(Process 3)

[0051] Compound (XXI) is reacted with optionally substituted aryl or optionally substituted heteroaryl having an acid halide (otherwise an active ester) group such as benzoyl chloride in a solvent such as dimethylformamide, dioxane, dimethylsulfoxide, acetonitrile, xylene, toluene, benzene or dichloromethane in the presence of a base (e.g., triethylamine, N-methylmorpholine or potassium carbonate) to give the desired compound (XXII). This reaction is carried out at a temperature under ice-cooling to 100 °C, preferably room temperature to 60 °C, and is completed for 3 to 30 hours,

preferably 10 to 25 hours.

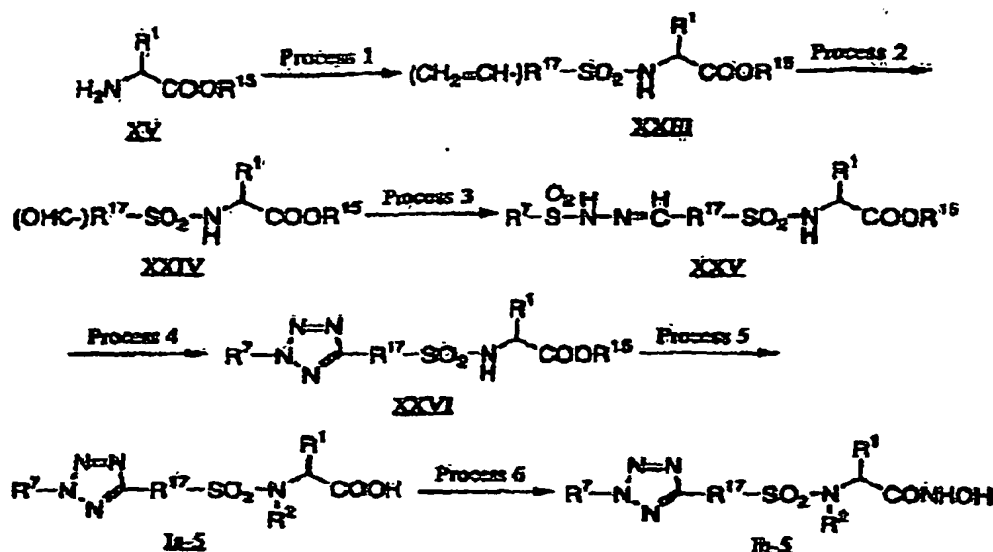
(Process 4)

[0052] This process may be carried out in the same manner as that described in process 1 of method A.

(Process 5)

[0053] This process may be carried out in the same manner as those described in processes 2 to 4 of method A.

# (Method E)



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>7</sup>, R<sup>15</sup>, R<sup>17</sup>, and Hal are as defined above.

[0054] Conversion of compound (XV) to compound (XXIII) is performed by sulfonating an amino group of the compound (XV) (process 1) in the same manner as that described in process 1 of method A. Conversion of compound (XXIII) to compound (XXIV) is done by the reduction wherein an ethenyl group of R<sup>13</sup> is converted into an aldehyde group (process 2). Conversion of compound (XXIV) to compound (XXVI) is performed by a tetrazole ring formation reaction (processes 3 and 4). Conversion of compound (XXVI) to compound (Ia-5) is N-alkylation, deprotection of a carboxyl protective group of compound (XXVI) (process 5), and this process can be carried out in the same manner as that described in process 1 of method A. Conversion of compound (Ia-5) to compound (Ib-5) is that of carboxylic acid derivatives to hydroxamic acid derivatives (process 6), which can be carried out in the same manner as those described in process 2 to 4 of method A. Each process will hereinafter be described in more detail

(process 1)

[0055] This process may be carried out in the same manner as that described in process 1 of method A.

(Process 2)

[0056] A compound (XIII) is treated with ozone in a solvent such as dichloromethane, ethyl acetate or methanol to form an oxonide, and then a reagent such as zinc-acetic acid, triethylphosphate or dimethylsulfide is added to this reaction mixture for reduction to give the desired aldehyde derivatives (XXIV). The reduction can also be carried out by catalytic hydrogenation. This reaction is carried out at 100 °C to room temperature, preferably -78 °C to a temperature

under ice-cooling, and is completed for 0.5 to 10 hours, preferably 1 to 3 hours.

(Process 3)

[0057] A compound (XXIV) is reacted with benzenesulfonylhydrazide in a solvent such as tetrahydrofuran or ether mixed with a solvent such as methanol or ethanol to give the desired compound (XXV). This reaction is carried out at a temperature under ice-cooling to 80°C, preferably room temperature to 50 °C and is completed for 3 to 30 hours, preferably 10 to 20 hours.

(Process 4)

[0058] Optionally substituted aryl or optionally substituted heteroaryl having amino group such as aniline is dissolved in a mixed solvent such as alcohol (e.g., ethanol) and water. To this mixture conc. hydrochloric acid and a diazotizing agent such as a sodium nitrite aqueous solution are added at -20°C to 10°C, preferably 0°C to 5 °C, to give a diazonium salt. The reaction time is 5 min to 1 hr, preferably 10 to 30 min. This reaction mixture is added to a pyridine solution of compound (XXV) and allowed to react for 1 to 10 hr, preferably 2 to 5 hr, at -30 °C to 50 °C, preferably - 15 °C to room temperature to give the desired compound (XXVI). When optionally substituted aryl or optionally substituted heteroaryl has a substituent(s) interfering with this reaction, the substituent(s) can previously be protected in accordance with a method of Protective Groups in Organic synthesis" (Theodora W. Green (John Wiley & Sons)), and then deprotected at an appropriate step.

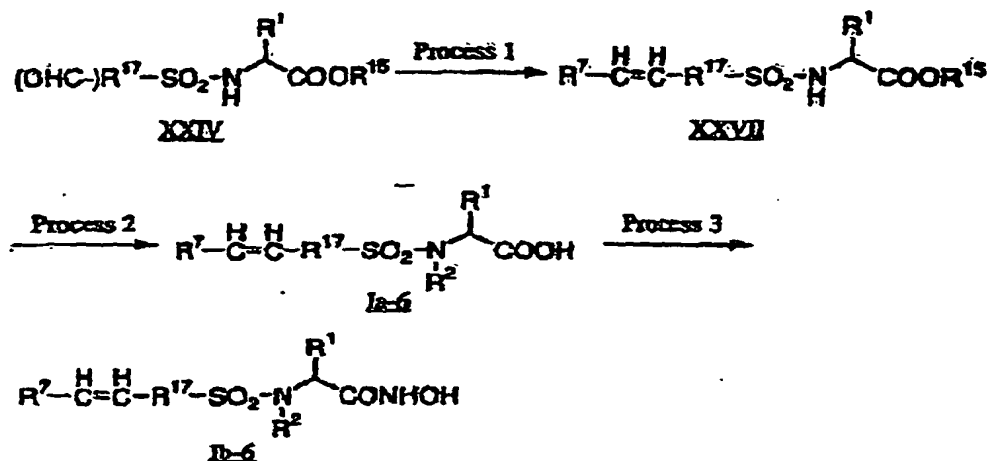
(Process 5)

[0059] This process may be carried out in the same manner as that described in process 1 of method A.

(Process 6)

[0060] This process may be carried out in the same manner as those described in processes 2 to 4 of method A.

#### (Method F)



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>7</sup>, R<sup>16</sup>, R<sup>17</sup>, and Hal are as defined above.

[0061] Conversion of compound (XXIV) to compound (XXVII) is performed by Wittig reaction (G. Wittig et al., Chem. Berr. 87, 1318 (1954)) wherein an aldehyde group of R<sup>17</sup> is utilized to introduce aryl or heteroaryl through a double bond (process 1). Conversion of compound (XXVII) to compound (Ia-6) is N-alkylation, deprotection of compound (XXVII) (process 2), and this process can be carried out similar as described in process 1 of method A. Conversion of compound (Ia-6) to compound (Ib-6) is that of carboxylic acid derivatives to hydroxamic acid derivatives (process 3), and this process can be carried out in the same manner as those described in processes 2 to 4 of method A. Each process will hereinafter be described in more detail.

(process 1)

[0062] Compound (XXIV) is reacted with ylide derivatives of optionally substituted aryl or optionally substituted heteroaryl such as  $P_3P=CHPh$ , which is produced by an usual method, in a solvent such as toluene, xylene, tetrahydrofuran, ether or dimethylformamide at -100 °C to room temperature, preferably -78 °C to ice-cooling for 1 to 20 hours, preferably 1 to 6 hours, to give the desired compound (XXVII). When optionally substituted aryl or optionally substituted heteroaryl has a substituent(s) interfering with this reaction, the substituent(s) can previously be protected in accordance with a method of "Protective Groups in Organic Synthesis" (Theodora W. Green (John Wiley & Sons)), and deprotected at an appropriate step.

(Process 2)

[0063] This process may be carried out in the same manner as that described in process 1 of method A.

(Process 3)

[0064] This process may be carried out in the same manner as those described in processes 2 to 4 of method A.

[0065] The term "compound of the present invention" herein used includes pharmaceutically acceptable salt or hydrate of the compound. The salt is exemplified by a salt with alkali metals (e.g., lithium, sodium, and potassium), alkaline earth metals (e.g., magnesium and calcium), ammonium, organic bases, amino acids, mineral acids (e.g., hydrochloric acid, hydrobromic acid, phosphoric acid, and sulfuric acid), or organic acids (e.g., acetic acid, citric acid, maleic acid, fumaric acid, benzenesulfonic acid, and p-toluenesulfonic acid). These salts can be formed by the usual method.

[0066] The compound of the present invention is not restricted to any particular isomers but includes all possible isomers and racemic modifications.

[0067] The compound of the present invention has an excellent activity for inhibiting metalloproteinase, especially activity for inhibiting MMP, and inhibits matrix dissolution, as described in the following test example. Therefore, the compound of the present invention is useful to treat or prevent diseases which are caused by MMP and relative enzymes such as TNF- $\alpha$  converting enzyme.

[0068] Definitely, the compounds of the present invention are useful in the prevention or treatment of diseases such as osteoarthritis, rheumatoid arthritis, corneal ulceration, periodontal disease, metastasis and invasion of tumor, advanced virus infection (e.g., HIV), arteriosclerosis obliterans, arteriosclerotic aneurysm, atherosclerosis, restenosis, sepsis, septic shock, coronary thrombosis, aberrant angiogenesis, scleritis, multiple sclerosis, open angle glaucoma, retinopathies, proliferative retinopathy, neovascular glaucoma, pterygium, keratitis epidermolysis bullosa, psoriasis, diabetes, nephritis, neurodegenerative disease, gingivitis, tumor growth, tumor angiogenesis, ocular tumor, angiofibroma, hemangioma, fever, hemorrhage, coagulation, cachexia, anorexia, acute infection, shock, autoimmune disease, malaria, Crohn disease, meningitis, and gastric ulcer.

[0069] When the compound of the present invention is administered to a person for treatment or prevention of the above diseases, they can be administered by oral administration such as powder, granules, tablets, capsules, pilulae, and liquid medicine, or by parenteral administration such as injections, suppository, percutaneous formulations or insufflation. An effective dose of the compound of the invention is formulated by being mixed with medicinal admixture such as excipient, penetrant, disintegrators or lubricant if necessary. When parenteral injection is prepared, the compound of the invention and an appropriate carrier are sterilized to prepare it.

[0070] An appropriate dosage varies with the conditions of the patients, an administration route, their age, their body weight and the like and should be determined by a physician in the end. In the case of oral administration, a daily dosage can generally be between 0.1 - 100 mg/kg/day, preferably 1 - 20 mg/kg/day. In the case of parenteral administration, the daily dosage can generally be between 0.01 - 10 mg/kg/day, preferably 0.1 - 1 mg/kg/day. The daily dosage can be administered in one to several divisions.

[0071] The following examples are provided to further illustrate the present invention and are not to be construed as limiting the scope thereof.

[0072] Abbreviations described below are used in the following examples. p-TaOH : p-toluenesulfonic acid.

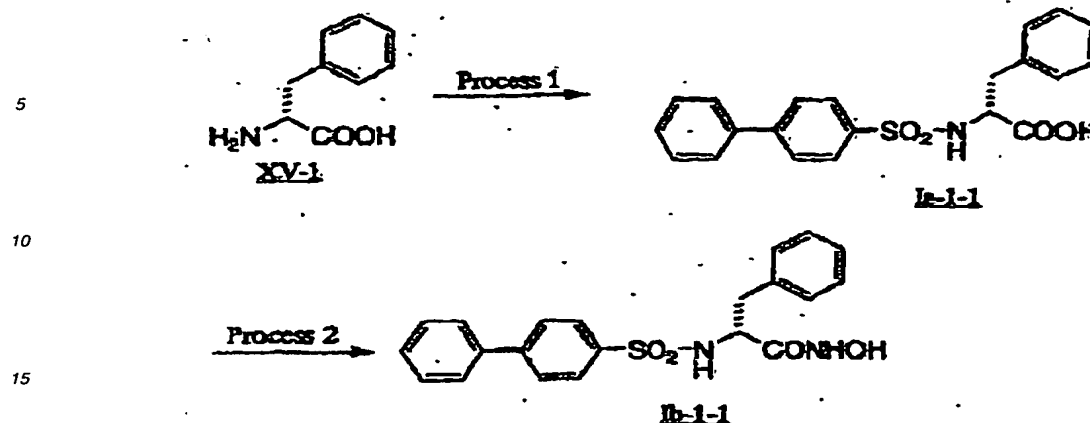
DMSO: dimethylsulfoxide

Me : methyl

<sup>t</sup>Bu: tert-butyl

Reference Example 1 (Method A)

[0073]



[0074] A suspension of (R)-(+)-phenylalanine (compound XV-1, 1.65g (10 mmol)) in 50 ml of dimethylformamide and 35 ml of water was stirred and treated with 2.78 ml (20 mmol) of triethylamine under ice-cooling. Then, 2.52g (10 mmol) of 4-biphenylsulfonyl chloride in 10 ml of dimethylformamide was added dropwise to the mixture over 5 min. After the reaction mixture was stirred for 2 h at the same temperature, 1.35 g (10 mmol) of 1-hydroxybenzotriazole hydrate, 2.1 g (11 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 3.47 g (50 mmol) of hydroxylamine hydrochloride, and 7 ml (50 mmol) of triethylamine were added to the mixture. After being stirred for 16 h at room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 2N HCl, 5% NaHCO<sub>3</sub>, and water, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with CHCl<sub>3</sub> / MeOH = 40/1 to 20/1 were collected to yield 1.70 g of compound (Ib-1-1) as a foam. Yield 43%. mp. 169-170°C.

Elemental analysis (%) C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>S

Calcd. : C; 63.62, H; 5.08, N; 7.07, S; 8.09

Found : C; 63.61, H; 5.12, N; 6.98, S; 8.06

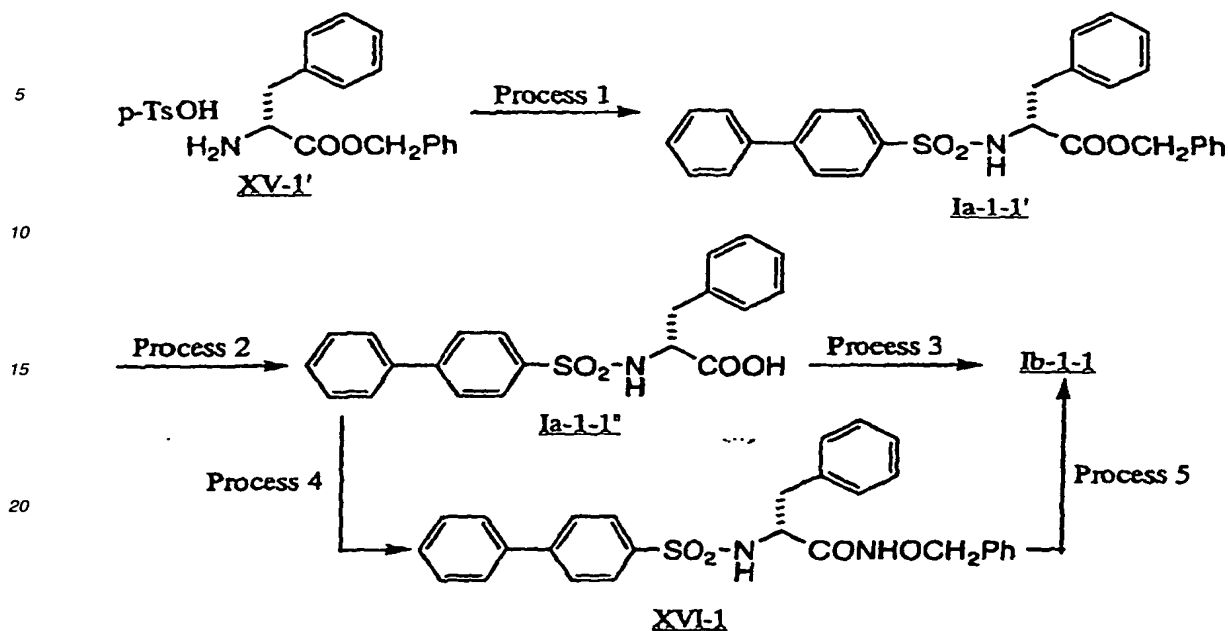
IR v max (cm<sup>-1</sup>) (Nujol) : 3365, 3295, 3266, 1674, 1320, 1159.

NMR (δ ppm) d<sub>6</sub> DMSO : 2.61 (dd, J=8.6, 13.4 Hz, 1H), 2.80 (dd, J=6.0, 13.6 Hz, 1H), 3.80 (m, 1H).

[α]<sub>D</sub><sup>25</sup> : +18.5 ± 1.2 (c=0.503 %, 25°C, DMSO)

Reference Example 1'

[0075] Another synthetic method of compound (Ib-1-1)



## Process 1

**[0076]** To a solution of (R)-phenylalanine benzyl ester tosylate (compound XV-1', 2.5 g (5.85 mmol)) in 60 ml of dichloromethane was added triethylamine (1.8 ml, 12.87 mmol) and 4-biphenylsulfonyl chloride (1.63 g, 6.44 mmol) under ice-cooling. After being stirred for 2 h at room temperature, the reaction mixture was washed with 2N HCl, 5% NaHCO<sub>3</sub> and water, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with CHCl<sub>3</sub> / MeOH = 40/1 to 20/1 were collected and crystallized from dichloromethane / hexane to give 2.32 g of compound (Ia-1-1'). Yield 84.1%. mp. 130-131°C.

Elemental analysis (%) C<sub>28</sub>H<sub>25</sub>NO<sub>4</sub>S

Calcd.: C; 71.32, H; 5.34, N; 2.97, S; 6.80

Found: C; 71.05, H; 5.41, N; 3.00, S; 6.81

IR v max (cm<sup>-1</sup>) (Nujol): 3352, 1732, 1341, 1190, 1163.

NMR (δ ppm) (CDCl<sub>3</sub>): 3.06 (d, J=5.8Hz, 2H), 4.30 (dt, J=6.0, 9.0Hz, 1H), 4.89 (s, 2H), 5.12 (d, J=9.0Hz, 1H), 6.98-7.81 (m, 14H).

[α]<sub>D</sub>: -16.4 ± 1.1 (c=0.506%, 25°C, MeOH)

## Process 2

**[0077]** A solution of compound (Ia-1-1') (2.23 g) which was obtained in process 1 in 50 ml of mixed solvents of methanol / ethyl acetate = 1/1, was hydrogenated using 10 % Pd/C (200 mg) for 25 min. The reaction mixture was filtered off, and the filtrate was concentrated in vacuo. The residue was recrystallized from dichloromethane/hexane to give 1.83 g of compound (Ia-1-1''). Yield 99.1 %. mp. 146-147°C.

Elemental analysis (%) C<sub>21</sub>H<sub>19</sub>NO<sub>4</sub>S

Calcd.: C; 66.12, H; 5.02, N; 3.67, S; 8.41

Found: C; 65.97, H; 5.06, N; 3.61, S; 8.48

IR v max (cm<sup>-1</sup>) (Nujol): 3408, 3305, 1751, 1325, 1161, 1134.

NMR (δ ppm) (CDCl<sub>3</sub>): 2.97 (dd, J=7.0, 13.8Hz, 1H), 3.14 (dd, J=5.2, 14.0Hz, 1H), 4.13 (m, 1H), 7.03-7.78 (m, 14H).

[α]<sub>D</sub>: -4.0 ± 0.4 (c=1.000 %, 25°C, MeOH)



## EP 0 950 656 B1

### Process 3

[0078] To a solution of compound (Ia-1-1", 1.0 g (2.62 mmol)) which was obtained in process 2 in dichloromethane (20 ml) was added 0.33 ml (3.93 mmol) of oxalyl chloride and one drop of dimethylformamide. After being stirred for 1 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in 10 ml of tetrahydrofuran. A solution of hydroxylamine hydrochloride (911 mg (13.1 mmol)) and NaHCO<sub>3</sub> 1.54 g (18.34 mmol) in 10 ml of tetrahydrofuran and 10 ml of water was stirred for 5 min under ice-cooling. To the mixture was added the above solution of acid chloride in tetrahydrofuran and the resulting mixture was stirred for 30 min. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with 5% NaHCO<sub>3</sub>, and water, and concentrated in vacuo to give compound (Ia-1) (969 mg). Yield 93.3%.

### Process 4

[0079] To a solution of compound (Ia-1-1", 2.0 g, 5.24 mmol) which was obtained in process 2 in dimethylformamide (20 ml) was added 1-hydroxybenzotriazole hydrate (0.7 g, 5.24 mmol), N-methylmorpholine (2.9 ml, 26.2 mmol), 1-ethyl-3-(3-diisopropylamino) carbodiimide hydrochloride (8 mmol), and O-benzylhydroxylamine hydrochloride (1.67 g, 10.48 mmol), and the resulting mixture was stirred for 6 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 2N HCl, 6% NaHCO<sub>3</sub>, and water, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with CH<sub>2</sub>Cl<sub>2</sub> / hexane = 1/1 were collected and recrystallized from dichloromethane/hexane to give 2.04 g of compound (XVI-1). Yield 80 %. mp. 171-173°C.

Elemental analysis (%) C<sub>28</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S

Calcd.: C: 69.12, H: 5.39, N: 5.76, S: 6.69

Found: C: 68.85, H: 5.46, N: 5.76, S: 6.78

IR v max (cm<sup>-1</sup>) (Nujol) : 3246, 1661, 1694, 1333, 1163.

NMR (δ ppm) (CDCl<sub>3</sub>): 2.85-3.60 (m, 2H), 3.85 (m, 1H), 4.77 (ABq-Apart, J=11.4Hz, 1H), 4.82 (ABq-Bpart, J=11.4Hz, 1H), 5.00 (m, 1H), 6.96-7.70 (m, 19H).

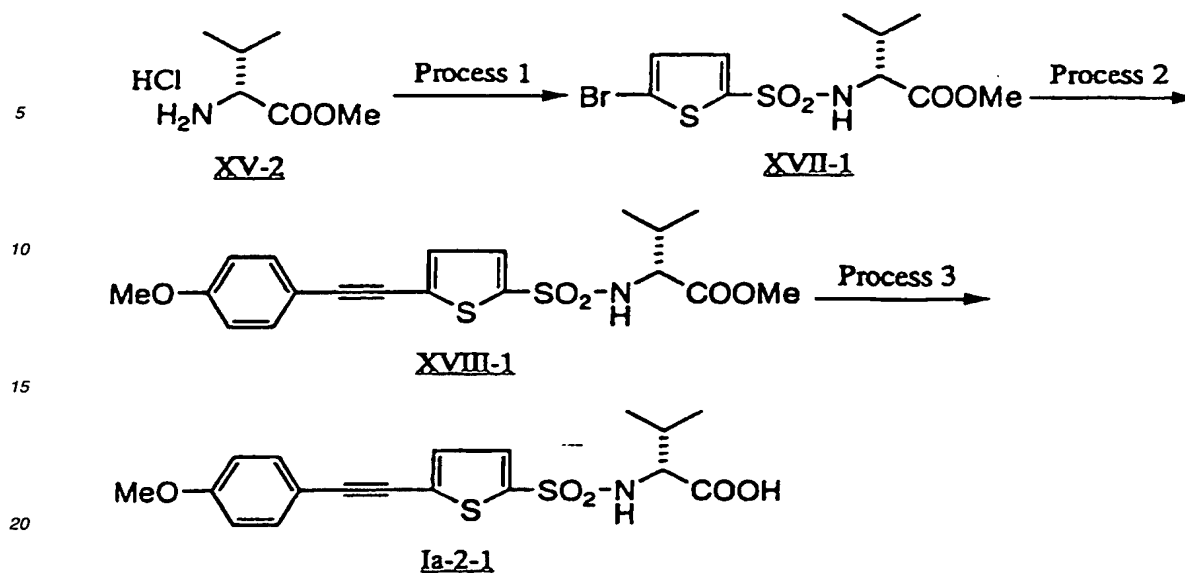
[α]<sub>D</sub>: -40.2 ± 1.6 (c=0.505%, 25°C, DMSO)

### Process 5

[0080] A solution of compound (XVI-1) (1.97 g) which was obtained in process 4 in 80 ml of mixed solvents of methanol / ethyl acetate = 1/1 was hydrogenated using 10 % Pd-C (200 mg) for 3.5 h. The reaction mixture was filtered off, and the filtrate was concentrated in vacuo. The residue was recrystallized from dichloromethane/hexane to give 1.35 g of compound (Ib-1-1). Yield 84.4 %.

### Example 92 (Method B)

[0081]



## Process 1

[0082] To a solution of D-valine methylester hydrochloride (XV-2) (755 mg, 4.5 mmol) in dichloromethane (12 ml) was added N-methylmorpholine (1.49 ml, 3×4.5 mmol) and 5-bromo-2-thiophensulfonyl chloride (1.24 g, 1.05×4.5 mmol) was added under ice-cooling. After being stirred for 15 h at room temperature, the reaction mixture was washed with 2N HCl, 5% NaHCO<sub>3</sub>, and water. The organic layer was concentrated in vacuo, and dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was subjected to silica gel column chromatography and the fractions eluting with ethyl acetate / hexane = 1/3 were collected and washed with n-hexane to give 1.32 g of the desired compound (XVII-1). Yield 82 %. mp. 109-110°C. Elemental analysis C<sub>10</sub>H<sub>14</sub>BrNO<sub>4</sub>S<sub>2</sub>

Calcd. : C; 33.71 H; 3.96 Br; 22.43 N; 3.93 S; 18.00

Found : C; 33.75 H; 3.89 Br; 22.43 N; 3.96 S; 17.86

[α]<sub>D</sub>: -34.5±0.7(c=1.012 CHCl<sub>3</sub> 25°C)

IR(CHCl<sub>3</sub>, ν max cm<sup>-1</sup>): 1737, 1356, 1164, 1138

NMR (CDCl<sub>3</sub>, δ ppm): 0.89(d, J=6.8 Hz, 3H), 1.00(d, J=6.8 Hz, 3H), 2.00 (m, 1H), 3.60(s, 3H), 3.83(dd, J=5.2, 10.0 Hz, 1H), 5.20(d, J=10.0 Hz, 1H), 7.04(d, J=4.1 Hz, 1H), 7.32(d, J=4.1 Hz, 1H)

## Process 2

[0083] To a degassed solution of 400 mg (1.12 mmol) of compound (XVII-1) in 5 ml of dimethylformamide was added 222 mg (1.5 × 1.12 mmol) of 4-methoxyphenylacetylene and 21 mg (0.1 × 1.12 mmol) of copper iodide (I) under an argon atmosphere. Then 39 mg (0.05 × 1.12 mmol) of bis(triphenylphosphine)palladium dichloride (II) and 0.47 ml (3 × 1.12 mmol) of triethylamine were added to the reaction mixture. The resulting mixture was degassed and stirred overnight under an argon atmosphere at 50 °C. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 1N HCl, 5 % NaHCO<sub>3</sub>, and water, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The resulting residue was column chromatographed on silica gel. The fractions eluting with n-hexane / ethyl acetate = 2/1 were collected and recrystallized from ethyl acetate / n-hexane to give 392 mg of the desired compound (XVIII-1). Yield 86 %. mp. 131-132°C. Elemental analysis C<sub>19</sub>H<sub>21</sub>NO<sub>5</sub>S<sub>2</sub>·0.2 H<sub>2</sub>O

Calcd. : C; 55.51 H; 5.25 N; 3.41 S; 15.60

Found : C; 55.80 H; 5.19 N; 3.38 S; 15.36

IR(KBr, ν max cm<sup>-1</sup>): 3268, 2203, 1736, 1604, 1524, 1348, 1164.

NMR(CDCl<sub>3</sub>, δ ppm): 0.90(d, J=6.6 Hz, 3H), 1.00(d, J=7.0 Hz, 3H), 2.00(m, 1H), 3.60(s, 3H), 3.84(s, 3H), 3.86(dd, J=5.0,

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10.2 Hz, 1H), 5.21(d, J=10.2 Hz, 1H). 6.90(d, J=9.0 Hz, 2H), 7.44(d, J=9.0 Hz, 2H), 7.12(d, J=4.0 Hz, 1H), 7.44(d, J=4.0 Hz, 1H).

### Process 3

**[0084]** To a solution of 407 mg (1 mmol) of compound (XVII-1) in 8 ml of tetrahydrofuran and 8 ml of methanol was added 5.1 ml of 1N NaOH. The resulting mixture was stirred for 6 h at 60 °C. The reaction mixture was concentrated in vacuo to remove an organic solvent, and the residue was diluted with ethyl acetate. The mixture was acidified with aqueous solution of citric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give 373 mg of compound (Ia-2-1). Yield 100%. mp. 147-148°C.  
IR (KBr,  $\nu$  max cm<sup>-1</sup>) : 1710, 1604, 1351, 1216.  
Elemental analysis C<sub>18</sub>H<sub>19</sub>NO<sub>5</sub>S<sub>2</sub> · 0.2H<sub>2</sub>O

Calcd. : C; 54.45 H; 4.92 N; 3.53 S; 16.15

Found : C; 54.39 H; 4.93 N; 3.79 S; 15.96

**[0085]** Examples 119-129, 136-156 shown in Tables 26, 27, 28, 29 and 30 were synthesized in a manner similar to those described in Example 92.

Table 26

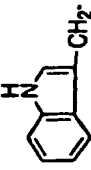


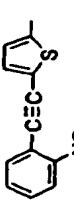

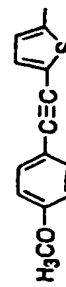
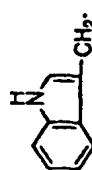

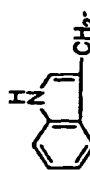
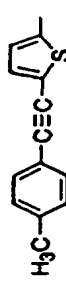
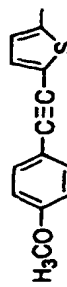
$\text{R}^1\text{B-SO}_2\text{NH-CH(R}^1\text{)-COOH (Ia)}$						
Example No.	R <sup>1</sup>	R <sup>18</sup>	*	mp (decomp.) (°C)	IR (ν cm <sup>-1</sup> ) (KBr)	Elemental analysis
119			R	167-169	1585, 1318 1153	-
120			R	-	1605, 1523 1340, 1151	-
121			R	-	1604, 1524 1336, 1173	-
122			R	103-106	1721, 1620 1339, 1163	-
123			R	180-182	1729, 1675 1340, 1168	-
124	(CH <sub>3</sub> ) <sub>2</sub> CH-		R	147-148	1710, 1604 1351, 1216	C <sub>18</sub> H <sub>19</sub> NO <sub>3</sub> S <sub>2</sub> ·0.2H <sub>2</sub> O Calc. C:54.45 H:4.92 N:3.53 S:16.15 Found. C:54.39 H:4.93 N:3.79 S:15.96

Table 27

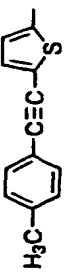

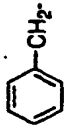
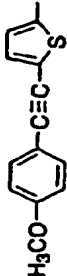
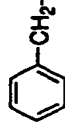

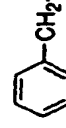

<div><math display="block">R^{18}\text{-SO}_2\text{NH}\overset{R^1}{\text{CH}}\cdot\text{COOH}\quad (\text{Ia})</math></div>						
Example No.	R <sup>1</sup>	R <sup>18</sup>	*	mp(decomp) (°C)	IR(v cm <sup>-1</sup> ) (KBr)	Elemental analysis
125	(CH <sub>3</sub> ) <sub>2</sub> CH-		R	157-158	1712, 1350 1163	C <sub>18</sub> H <sub>19</sub> NO <sub>4</sub> S <sub>2</sub> ·0.2H <sub>2</sub> O Calc. C:56.73 H:5.13 N:3.68 S:16.83 Foun.C:57.03 H:5.30 N:3.89 S:16.56
126	(CH <sub>3</sub> ) <sub>2</sub> CH-		R	154-156	1710, 1499 1356, 1165	-
127			R	149-150	1695, 1334 1184	C <sub>22</sub> H <sub>19</sub> NO <sub>5</sub> S <sub>2</sub> ·0.2H <sub>2</sub> O Calc. C:59.36 H:4.39 N:3.15 S:14.41 Foun.C:59.43H:4.61 N:3.25 S:14.02
128			R	161-164	1710, 1329 1180	-
129			R	155-158	1734, 1699 1324, 1105	C <sub>21</sub> H <sub>16</sub> FNO <sub>4</sub> S <sub>2</sub> Calc. C:58.73 H:3.75 F:4.42 N:3.26 S:14.93 Foun.C:58.66 H:3.93 F:4.52 N:3.33 S:14.41

Table 28

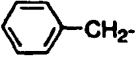
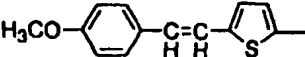
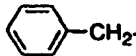
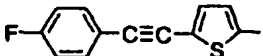
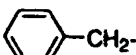
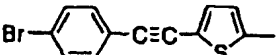
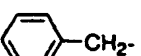
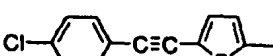
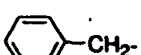
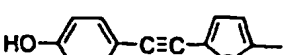
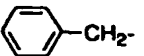
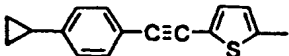
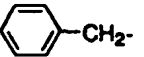
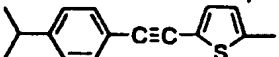
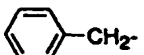
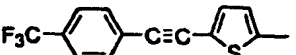
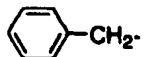
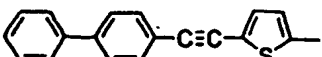
<div style="text-align: center;"> <math display="block">R^{18}-SO_2NH-\overset{\overset{R^1}{ }}{\underset{\underset{H}{ }}{C}}-COOH \quad (Ia)</math> </div>						
Example No.	R <sup>1</sup>	R <sup>18</sup>	*	mp (decomp.) (°C)	IR (ν cm <sup>-1</sup> ) (KBr)	Elemental analysis
136			R	-	-	-
137			R	-	-	-
138			R	-	-	-
139			R	-	-	-
140			R	-	-	-

Table 29

<div style="text-align: center;"> <math display="block">R^{18}-SO_2NH-\overset{\overset{R^1}{ }}{\underset{\underset{H}{ }}{C}}-COOH \quad (Ia)</math> </div>						
Example No.	R <sup>1</sup>	R <sup>18</sup>	*	mp (decomp.) (°C)	IR (ν cm <sup>-1</sup> ) (KBr)	Elemental analysis
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142			R	-	-	-
143			R	-	-	-
144			R	-	-	-

(continued)

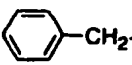
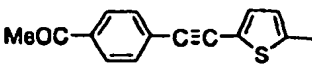
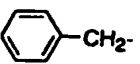
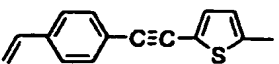
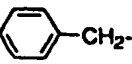
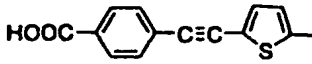
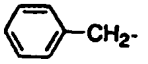
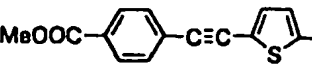
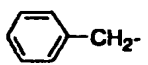
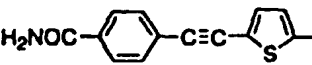
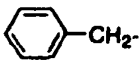
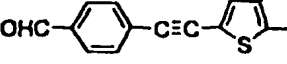
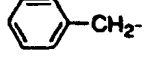
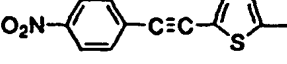
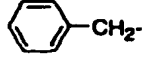
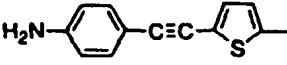
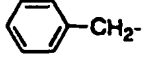
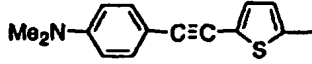
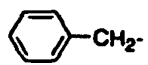
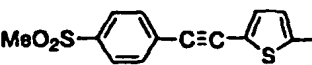
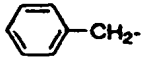
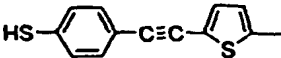
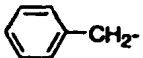
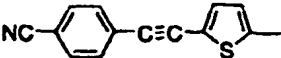
$\text{R}^{18}\text{-SO}_2\text{NH}\text{-}\overset{\text{R}^1}{\underset{\cdot}{\text{C}}}\text{-COOH} \quad (\text{Ia})$						
Example No.	R <sup>1</sup>	R <sup>18</sup>	*	mp (decomp.) (°C)	IR (ν cm <sup>-1</sup> ) (KBr)	Elemental analysis
145			R	-	-	-
146			R	-	-	-
147			R	-	-	-
148			R	-	-	-

Table 30

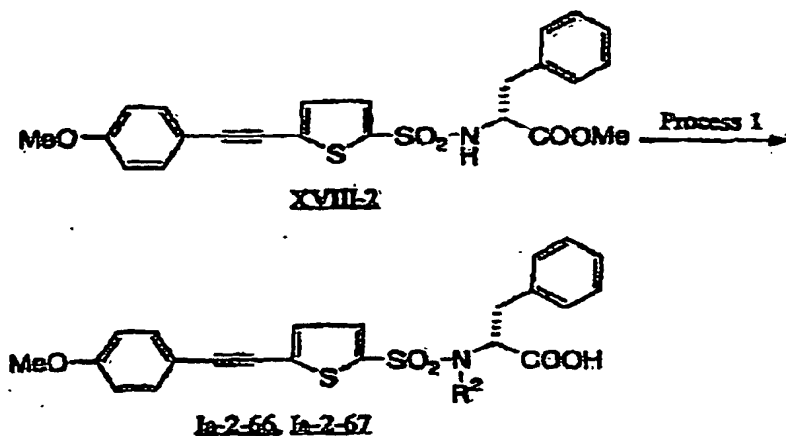
$\text{R}^{18}\text{-SO}_2\text{NH}\text{-}\overset{\text{R}^1}{\underset{\cdot}{\text{C}}}\text{-COOH} \quad (\text{Ia})$						
Example No.	R <sup>1</sup>	R <sup>18</sup>	*	mp (decomp.) (°C)	IR(ν cm <sup>-1</sup> ) (KBr)	Elemental analysis
149			R	-	-	-
150			R	-	-	-
151			R	-	-	-
152			R	-	-	-
153			R	-	-	-
154			R	-	-	-

(continued)

$\text{R}^{18}\text{-SO}_2\text{NH}\begin{array}{c} \text{R}^1 \\   \\ \text{COOH} \end{array} \quad (\text{Ia})$						
Example No.	R <sup>1</sup>	R <sup>18</sup>	*	mp (decomp.) (°C)	IR(ν cm <sup>-1</sup> ) (KBr)	Elemental analysis
155			R	-	-	-
156			R	-	-	-

Example 157, 158

[0086]

Process 1 (R<sup>2</sup>=CH<sub>3</sub>)

[0087] To a solution of 150 mg (0.33 mmol) of compound (XVIII-2) in 2 ml of dimethylformamide which was synthesized in the same manner as those described in Example 96 was added 227 mg (5 x 0.33 mmol) of potassium carbonate and 0.1 ml (5 x 0.33 mmol) of methyl iodide, and the resulting mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give 373 mg of N-methyl derivative as an oil. Yield 91%. Elemental analysis C<sub>24</sub>H<sub>23</sub>NO<sub>5</sub>S<sub>2</sub>

Calcd : C; 61.39 H; 4.94 N; 2.98 S; 13.66  
Found: C; 61.22 H; 5.18 N; 2.98 S; 13.27

[0088] Further, a solution of 140 mg of the above oily compound which was obtained in the above process in 2 ml of methanol was added 0.6 ml of 1N NaOH, and the resulting mixture was stirred overnight at room temperature. The reaction mixture was acidified with 2N HCl and extracted with ethyl acetate. The organic layer was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give 105 mg of compound (Ia-2-68) (R=Me). Yield 77%. mp. 185-186°C. Elemental analysis C<sub>22</sub>H<sub>21</sub>NO<sub>3</sub>S



Calcd. : C; 60.64 H; 4.65 N; 3.07 S; 14.08

Found : C; 60.56 H; 4.84 N; 3.01 S; 13.94.

IR (KBr,  $\nu$  max  $\text{cm}^{-1}$ ): 3600-2300br. 3426, 2203. 1710, 1604, 1503, 1344, 1161.

<sup>1</sup>H NMR ( $\text{d}_6$ -DMSO  $\delta$  ppm): 2.88(s, 3H), 2.93(dd,  $J=12.0, 10.2$  Hz, 1H), 3.19 (dd,  $J=14.2, 5.6$  Hz, 1H), 3.81(s, 3H), 4.74 (dd,  $J=5.4, 10.2$  Hz, 1H), 6.99-7.04(m, 2H), 7.20-7.35(m, 7H), 7.52-7.56(m, 2H), 6.90(d,  $J=9.0$  Hz, 2H), 7.44(d,  $J=9.0$  Hz, 2H), 7.12(d,  $J=4.0$  Hz, 1H), 7.44(d,  $J=4.0$  Hz, 1H).

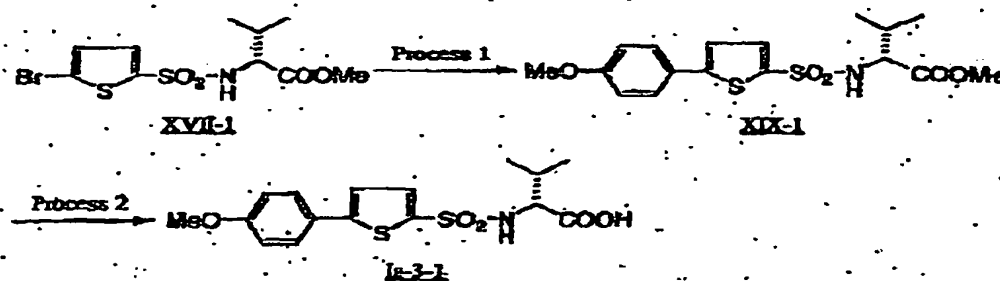
[0089] The compound (Ia-2-67) ( $\text{R}^2 = \text{CH}_2\text{Ph}$ ) was synthesized in the same manner as those described in Example 157.

IR(KBr,  $\nu$  max  $\text{cm}^{-1}$ ): 2200, 1722, 1340, 1151.

<sup>1</sup>H NMR ( $\text{d}_6$ -DMSO,  $\delta$  ppm) : 2.94(dd,  $J=7.6, 13.8$  Hz, 1H), 3.19(dd,  $J=7.2, 14.4$  Hz, 1H), 3.83(s, 3H), 4.29(d,  $J=16.2$  Hz, 1H), 4.62(d,  $J=16.2$  Hz, 1H) (Only characteristic peaks are shown).

Reference Example 159 (Method C)

[0090]



Process 1

[0091] To a solution of 500 mg (1.4 mmol) of compound (XVII-2) which was obtained in Example 96 in 12 ml of dry tetrahydrofuran was added 337 mg (2 x 1.4 mmol) of powdery potassium carbonate, 319 mg (1.5x1.4 mmol) of 4-methoxyphenylboronic acid and 81 mg (0.05 x 1.4 mmol) of tetrakis(triphenylphosphine)palladium. The resulting mixture was stirred under argon atmosphere for 48 h at 75°C. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 1N HCl, 5%  $\text{NaHCO}_3$  aq., and water, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The residue was column chromatographed on silica gel. The fractions eluting with n-hexane / ethyl acetate = 3/1 were collected and recrystallized from n-hexane / ethyl acetate = 3/1 to give 447 mg of the desired compound (XIX-1). Yield 83%. mp. 122-123°C.

Elemental analysis  $\text{C}_{17}\text{H}_{21}\text{NO}_5\text{S}_2$

Calcd : C; 53.25 H; 5.52 N; 3.65 S; 16.72

Found: C; 53.26 H; 5.50 N; 3.69 S; 16.63

$[\alpha]_D -21.7 \pm 0.6$  ( $c=1.000$  DMSO 25°C)

IR (KBr,  $\nu$  max  $\text{cm}^{-1}$ ) : 1735, 1605, 1505, 1950, 1167, 1136

<sup>1</sup>H NMR ( $\text{CDCl}_3$ ,  $\delta$  ppm): 0.90(d,  $J=7.0$  Hz, 3H), 1.00(d,  $J=6.6$  Hz, 9H), 2.10(m, 1H), 3.54(s, 3H), 3.35(s, 8H), 3.87(dd,  $J=5.0, 10.2$  Hz, 1H), 5.20(d,  $J=10.2$  Hz, 1H), 6.94(d,  $J=9.0$  Hz, 2H), 7.52(d,  $J=9.0$  Hz, 2H), 7.11(d,  $J=4.0$  Hz, 1H), 7.49 (d,  $J=4.0$  Hz, 1H).

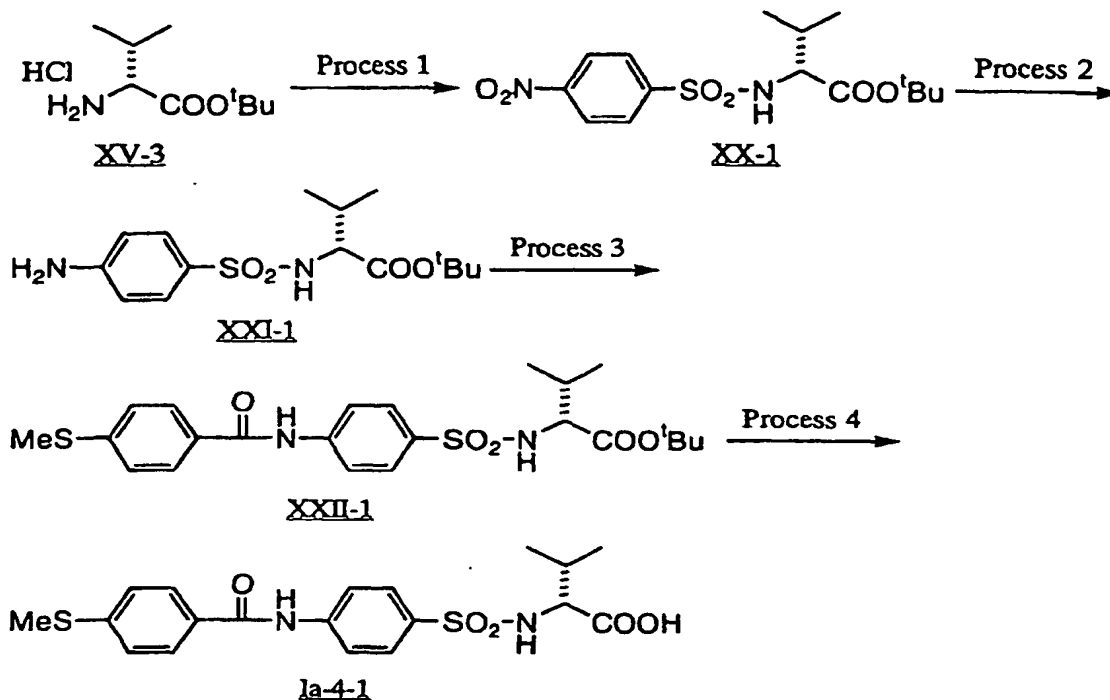
Process 2

[0092] To a solution of 390 mg (1.01 mmol) of compound (EX-1) in 8ml of tetrahydrofuran and 8ml of methanol was added 5.1 ml of 1N NaOH, and the resulting mixture was stirred at 60°C for 6 h. The reaction mixture was concentrated in vacuo to remove an organic solvent. The resulting residue was diluted with ethyl acetate. The mixture was acidified with aqueous solution of citric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo to give 373 mg of compound (Ia-3-1). Yield 100% mp. :174-176°C

IR(KBr,  $\nu$  max  $\text{cm}^{-1}$ ) : 1735, 1503, 1343, 1163.

Reference Example 176 (Method D)

[0093]



## Process 1

[0094] To a solution of 10 g (47.68 mmol) of D-valine tert-butyl ester hydrochloride (XV-3) in 100 ml of dichloromethane was added 15.7 ml (3 x 47.68 mmol) of N-methylmorpholine and 14.1 g (1.2 x 47.68 mmol) of 4-nitrobenzenesulfonyl chloride under ice-cooling. After being stirred for 5 h at room temperature the reaction mixture was washed with 2N HCl, 5% NaHCO<sub>3</sub>, water. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo, and the resulting residue was recrystallized from dichloromethane / n-hexane to give 13.3g of the desired compound (XX-1). Yield 77.8%. mp. 89-90°C.

Elemental analysis C<sub>15</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>S

Calcd. : C; 50.27 H; 6.19 N; 7.82 S; 8.95

Found : C; 50.04 H; 6.10 N; 7.89 S; 8.84

[α]<sub>D</sub> -2.9±0.8(c=0.512 DMSO 23°C)

IR(KBr, ν max cm<sup>-1</sup>) : 3430br, 3301, 1722, 1698, 1525, 1362, 1348, 1181, 1174, 1159.

## Process 2

[0095] A solution of 13.29 g (37.08 mmol) of compound (XX-1) in 200 ml of methanol was hydrogenated using 10% Pd/C (1g) for 2h at room temperature. The reaction mixture was filtered off and the filtrate was concentrated in vacuo. The residue was recrystallized from acetone/ n-hexane to give 11.5g of amine derivative (XXI-1). Yield 84.4%. mp. 164-166°C

Elemental analysis C<sub>15</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>S

Calcd. : C; 54.86 H; 7.37 N; 8.53 S; 9.76

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Found : C; 54.84 H; 7.33 N; 8.63 S; 9.50

$[\alpha]_D +10.3 \pm 1.0 (c=0.515 \text{ DMSO } 23^\circ\text{C})$

IR(KBr,  $\nu$  max  $\text{cm}^{-1}$ ) : 3461, 3375, 1716, 1638, 1698, 1344, 1313.

5 NMR( $d_6$ -DMSO,  $\delta$  ppm) : 0.80(d, J=6.8 Hz, 3H), 0.82(d, J=6.6 Hz, 3H), 1.28(s, 9H), 1.83(m, 1H), 3.80(m, 1H), 5.86(s, 2H), 6.56(d, J=8.8 Hz, 2H), 7.36(d, J=8.6 Hz, 2H), 7.47(d, J=9.6 Hz, 1H)

### Process 3

10 [0096] To a solution of 828 mg (1mmol) of compound (XXI-1) in 10 ml of dichloromethane was added 0-33 ml (3 x 1 mmol) of N-methylmorpholine and 280 mg (1.5 x 1 mmol) of 4-(methylthio)benzoyl chloride under ice-cooling The reaction mixture was stirred overnight at room temperature. To the reaction was added ethyl ether and precipitates were collected and washed with ice-water and ethyl ether, The solids were recrystallized from acetone/ethyl ether to give 433 mg of the desired compound (XXII-1). Yield 90.5%, mp. 235-238°C.

15 Elemental analysis  $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_5\text{S}_2$

Calcd. : C; 57.72 H; 6.32 N; 5.85 S; 13.40

Found : C; 57.63 H; 6.28 N; 5.86 S; 13.20

20  $[\alpha]_D +5.7 \pm 0.8 (c=0.512 \text{ DMSO } 25^\circ\text{C})$

IR(KBr,  $\nu$  max  $\text{cm}^{-1}$ ): 3366, 3284, 1713, 1667, 1592, 1514, 1498, 1341, 1317.

NMR( $d_6$ -DMSO,  $\delta$  ppm) : 0.82(d, J=6.6 Hz, 3H). 0.84(d, J=6.8 Hz, 3H), 1.22(s, 9H), 1.91(m, 1H), 2.55(s, 3H), 3.32(s, 3H), 3.44(dd, J=6.2, 8.6 Hz, 1H), 7.40(d, J=8.6 Hz, 2H), 7.78(d, J=8.6 Hz, 2H), 7.80.8.01(m, 5H), 10.48 (s, 1H).

### 25 Process 4

[0097] To a solution of 405 mg (0.85 mmol) of compound (XXII-1) in 3 ml of dichloromethane was added 3.3 ml (50 x 0.85 mmol) of trifluoroacetic acid and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated in vacuo and the resulting residue was washed with ethyl ether to give 340 mg of the desired compound (Ia-4-1). Yield 94.7%. mp. 231-234°C

30 IR(KBr,  $\nu$  max  $\text{cm}^{-1}$ ) : 1748, 1655, 1592. 1323, 1161.

Elemental analysis  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_5\text{S}_2 - 0.1\text{CF}_3\text{COOH}$

Calcd. : C; 63.14 H; 6.13 N; 6.46 S; 14.78

35 Found :C; 53.48 H; 5.31 N; 6.57 S; 15.06

### Reference Example 209 (Method E)

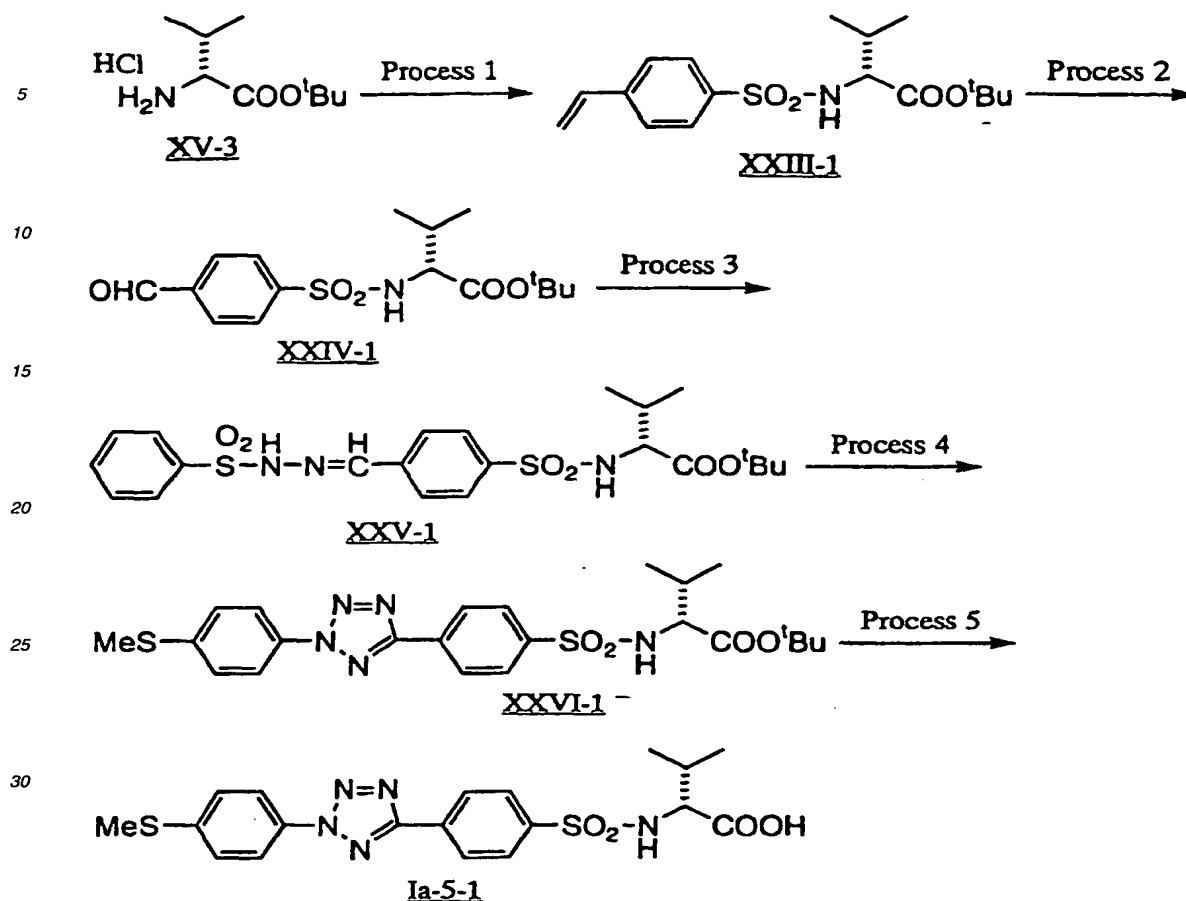
[0098]

40

45

50

55



## Process 1

[0099] To a solution of 20.94 g (99.8 mmol) of D-valine tert-butyl ester hydrochloride (XV-3) in 200 ml of dichloromethane was added 22 ml (2 x 99.8 mmol) of N-methylmorpholine and 20.27 g (99.8 mmol) of p-styrenesulfonyl chloride under ice-cooling. After being stirred for 15 h at room temperature, the reaction mixture was washed with 2N HCl, 5% NaHCO<sub>3</sub>, water. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo, and the resulting residue was column chromatographed on silica gel. The fractions eluting with ethyl acetate / n-hexane / chloroform = 1/3/1 were collected and washed with n-hexane to give 28.93 g of the desired compound (XXIII-1). Yield 85 %. mp. 118-120°C.

IR(KBr,  $\nu$  max cm<sup>-1</sup>): 3419, 3283, 1716, 1348, 1168.

NMR(CDCl<sub>3</sub>,  $\delta$  ppm): 0.85(d, J=6.9 Hz, 3H), 1.00(d, J=6.6 Hz, 3H), 1.21(s, 9H), 2.04(m, 1H), 3.62(dd, J=9.8, 4.5 Hz, 1H), 5.09(d, J=9.8 Hz, 1H), 5.41(dd, J=0.5, 10.9 Hz, 1H), 5.84(dd, J=0.5, 17.6 Hz, 1H), 6.72(dd, J=10.9, 17.6 Hz, 1H), 7.49(d, J=8.4 Hz, 2H), 7.79(d, J=8.4 Hz, 2H).

## Process 2

[0100] Ozone gas was bubbled through a solution of 5.09 g (15 mmol) of compound (XXIII-1) in 300 ml of dichloromethane for 15 h at -78°C. To this solution was added 22 ml (20 x 15 mmol) of methylsulfide, and the reaction mixture was allowed to warm to room temperature gradually over 80 min and concentrated in vacuo to give 6.03g aldehyde derivative (XXIV-1).

IR(CHCl<sub>3</sub>,  $\nu$  max cm<sup>-1</sup>): 3322, 1710, 1351, 1170.

NMR(CDCl<sub>3</sub>,  $\delta$  ppm): 0.85(d, J=6.9 Hz, 3H), 1.00(d, J=6.9 Hz, 3H), 1.22(s, 9H), 2.07(m, 1H), 3.69(dd, J=4.5, 9.9 Hz, 1H), 8.01(s, 4H), 10.08(s, 1H).

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## Process 3

[0101] To a solution of 6.02 g (15 mmol) of compound (XXIV-1) in 60 ml of ethanol and 15 ml of tetrahydrofuran was added 2.72 g (1.05 x 15 mmol) of benzenesulfonyl hydrazide at room temperature. After being stirred for 2 h, the resulting mixture was concentrated in vacuo. The residue which was obtained by concentration in vacuo was column chromatographed on silica gel and the fractions eluting with chloroform / ethyl acetate = 1/4 were collected and recrystallized from ethyl acetate to give 4.44 g of the desired compound (XXV-1). Yield from process 2 60%. mp. 163-164°C.

Elemental analysis  $C_{22}H_{29}NaO_6S_2$

Calcd. : C; 53.32 H; 5.90 N; 8.48 S; 12.94

Found : C; 53.15 H; 5.87 N; 8.32 S; 12.82

$[\alpha]_D -11.6 \pm 1.0 (c=0.509 \text{ DMSO } 23.5^\circ\text{C})$

IR(KBr,  $\nu$  max  $\text{cm}^{-1}$ ) : 3430, 3274, 1711, 1364, 1343, 1172.

NMR( $\text{CDCl}_3$ ,  $\delta$  ppm) : 0.84(d, J=6.9 Hz, 3H), 0.99(d, J=6.6 Hz, 3H), 1.19(s, 9H), 2.00(m, 1H), 3.63(dd, J=4.5, 9.9 Hz, 1H), 5.16(d, J=9.9 Hz, 1H), 7.50-7.68(m, 5H), 7.73(s, 1H), 7.78-7.84(m, 2H), 7.96-8.02(m, 2H), 8.16(brs, 1H).

## Process 4

[0102] To a solution of 0.14 ml (1.11 x 1 mmol) of 4-(methylmercapto)aniline and 0.3 ml of conc. hydrochloric acid in 3 ml of aqueous 50% ethanol solution was added a solution of 78.4 mg (1.14 x 1 mmol) of sodium nitrite in 1 ml of water at 0 to 5 °C of the internal temperature and the reaction mixture was stirred for 15 min at the same temperature. To a solution of 496 mg (1 mmol) of compound (XXV-1) in 5 ml of dry pyridine was added the above reaction mixture over 8 min at -25°C. This reaction mixture was stirred for additional 4 h at -15°C to rt, poured into water, and extracted with ethyl acetate. The organic layer was washed with 2N HCl, 5%  $\text{NaHCO}_3$ , and water, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The residue was column chromatographed on silica gel and the fractions eluting with chloroform / ethyl acetate = 1/9 were collected to give 374 mg of the desired compound (XXVI-1). Yield 74%.

Elemental analysis  $C_{23}H_{29}N_5O_4S_2 \cdot 0.3H_2O$

Calcd. : C; 54.27 H; 5.86 N; 13.76 S; 12.60

Found : C; 54.25 H; 5.77 N; 13.87 S; 12.52

IR(KBr,  $\nu$  max  $\text{cm}^{-1}$ ) : 3422, 3310, 1705, 1345, 1171.

NMR( $d_6$ -DMSO,  $\delta$  ppm) : 0.83(d, J=6.9 Hz, 3H), 0.86(d, J=7.2 Hz, 3H), 1.19(s, 9H), 2.00(m, 1H), 2.59(s, 3H), 3.54(dd, J=6.3, 9.6 Hz, 1H), 7.56(d, J=8.7 Hz, 2H), 8.00(d, J=8.6 Hz, 2H), 8.10(d, J=8.7 Hz, 2H), 8.33(d, J=9.6 Hz, 2H), 8.34(d, J=8.7 Hz, 2H).

## Process 5

[0103] A solution of 353 mg of compound (XXVI-1) in 2.5 ml of dichloromethane and 2.5 ml of trifluoroacetic acid was stirred for 3 h at room temperature. The reaction mixture was concentrated in vacuo and the resulting residue was washed with ethyl ether to give 308 mg of compound (Ia-5-1). Yield 98%. mp. 194 - 195°C.

IR(KBr,  $\nu$  max  $\text{cm}^{-1}$ ) : 1720, 1343, 1166.

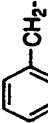

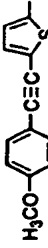
Elemental analysis  $C_{19}H_{21}N_5O_4S_2 \cdot 1.1H_2O$

Calcd. : C; 48.83 H; 5.00 N; 14.99 S; 13.72

Found : C; 49.13 H; 5.25 N; 14.55 S; 13.34

[0104] The compound which is shown in Table 45 was synthesized in a manner similar to those described in Example 157.

Table 45

Example No.	R <sup>1</sup>	R <sup>18</sup>	R <sup>19</sup>	R <sup>20</sup>	*	mp (decomp.) (°C)	IR (ν cm <sup>-1</sup> ) (KBr)	<sup>1</sup> H-NMR (δ ppm) d <sub>6</sub> -DMSO
263		 -C≡C- 	-(CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	-COOH	R	-	-	-

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[0105] Test examples of the compounds of the present invention are described below. The test compounds are the ones described in the Examples and Tables.

### Test example

#### (1) Isolation and purification of MMP-9 (92 kDa, gelatinase B)

[0106] Type IV collagenase (MMP-9) was purified according to the methods described in the following literature. Scott M. Wilhelm et al., J. Biol. Chem., 264, 17213-17221, (1989), SV40-transformed Human Lung Fibroblasts Secrete a 92-kDa Type IV Collagenase Which is Identical to That Secreted by Normal Human Macrophages; Yasunori Okeda et al., J. Biol. Chem., 267, 21712-21719, (1992). Matrix Metalloproteinase 9 (92-kDa Gelatinase/Type IV Collagenase) from HT 1080 Human Fibrosarcoma Cells; Robin V. Ward et al., Biochem. J., (1991) 278, 179-187. The purification of tissue inhibitor of metalloproteinase 2 from its 72 kDa progelatinase complex.

[0107] MMP-9 is secreted from human fibrosarcoma cell line ATCC HT 1080, into its culture medium when it is stimulated with 12-tetradecanoylphorbol-13-acetate (TPA). The production of MMP-9 in this culture was verified by the gelatin zymography as described in the following literature (Hidekazu Tanaka et al., (1993) Biochem. Biophys. Res. Commun. 190, 732-740, Molecular cloning and manifestation of mouse 105-kDa gelatinase cDNA). The conditioning medium of the stimulated HT 1080 was concentrated and was purified with gelatin-Sepharose 4B, concanavalin A-sepharose, and Sephacryl S-200. The purified pro-MMP-9 (92 kDa, gelatinase B) thus obtained gave a single positive band in the gelatin zymography. Subsequently, activated MMP-9 was obtained by treating the pro-MMP-9 with trypsin.

#### (2) Assay methods of type IV collagenase inhibitors

[0108] Collagenase assay was performed using the activated MMP-9 described above and the substrate supplied in the type IV collagenase activity kit (YAGAI, inc.), according to the manufacturer's protocol. The following 4 assays are performed per compound (inhibitor).

(A) substrate (type IV collagenase), enzyme (MMP-9), inhibitor

(B) substrate (type IV collagenase), inhibitor

(C) substrate (type IV collagenase), enzyme (MMP-9)

(D) substrate (type IV collagenase)

[0109] According to the manufacturer's protocol, fluorescent intensity was measured and percent inhibition was determined by the following equation.

$$\text{Inhibition (\%)} = \{1 - (A - B) / (C - D)\} \times 100$$

[0110] IC<sub>50</sub> is a concentration at which the percent inhibition reaches 50 %. The results are shown in Tables 47 to 54.

Table 47\*

Example No.	Compound No.	IC <sub>50</sub> (μM)	Compound No.	IC <sub>50</sub> (μM)
1	1a-1-1	0.24	1b-1-1	0.030
2	1a-1-2	2.6	1b-1-2	0.04
3	1a-1-3	0.18	1b-1-3	0.005
4	1a-1-4	2.25		
5	1a-1-5	0.81	1b-1-5	0.041
6	1a-1-6	0.68	1b-1-6	0.034
7			1b-1-7	0.028
8	1a-1-8	2.0	1b-1-8	2.0
9			1b-1-9	0.41
10			1b-1-10	2.1

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(continued)

Example No.	Compound No.	IC <sub>50</sub> (μM)	Compound No.	IC <sub>50</sub> (μM)
11			1b-1-11	1.7
12			1b-1-12	0.085
13			1b-1-13	0.38
14	1a-1-14	3.7	1b-1-14	0.11
15			1b-1-15	0.027
16	1a-1-16	0.520	1b-1-16	0.0108
17	1a-1-17	0.205	1b-1-17	0.0203
18	1a-1-18	0.500	1b-1-18	0.0282
20			1b-1-20	0.134
21	1a-1-21	4.65	1b-1-21	0.0041
23			1b-1-23	0.073
24			1b-1-24	0.2
26			1b-1-26	1.3
27			1b-1-27	3.0
30	1a-1-30	1.16	1b-1-30	0.213
31			1b-1-31	0.0129
* reference compounds, not included in the present invention				

Table 48\*

Example No.	Compound No.	IC <sub>50</sub> (μM)	Compound No.	IC <sub>50</sub> (μM)
33	1a-1-33	0.24	1b-1-33	0.005
35	1a-1-35	2.6	1b-1-35	0.0216
38	1a-1-38	0.018		
40	1a-1-40	0.076		
41	1a-1-41	0.312		
42	1a-1-42	0.0123		
43	1a-1-43	0.625		
44	1a-1-44	1.910		
45	1a-1-45	0.040		
46	1a-1-46	1.12		
47	1a-1-47	0.389		
48	1a-1-48	1.15		
49	1a-1-49	0.249		
50	1a-1-50	0.553		
51	1a-1-51	0.110		
52	1a-1-52	0.329		
53	1a-1-53	1.8		
54	1a-1-54	0.075		



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(continued)

Example No.	Compound No.	IC <sub>50</sub> (μM)	Compound No.	IC <sub>50</sub> (μM)
55	1a-1-55	0.0398		
60	1a-1-60	1.31	1b-1-60	0.0012
61	1a-1-61	0.247	1b-1-61	0.247
62			1b-1-62	3.50
63	1a-1-63	1.05	1b-1-63	0.00039
64	1a-1-64	1.90	1b-1-64	0.0037
65	1a-1-65	0.291	1b-1-65	0.0035
* reference compounds not included in the present invention				

Table 49\*

Example No.	Compound No.	IC <sub>50</sub> (μM)	Compound No.	IC <sub>50</sub> (μM)
67	1a-1-67		1b-1-67	0.0061
68	1a-1-68	0.231		
80	1a-1-80	1.91		
83	1a-1-83	1.77		
85	1a-1-85	1.2	1b-1-85	0.013
86	1a-1-86	0.35	1b-1-86	0.0053
87			1b-1-87	0.940
93	1a-2-2	0.237		
94	1a-2-3	0.0109		
95	1a-2-4	0.0759		
96	1a-2-5	0.123		
97	1a-2-6	0.088		
98	1a-2-7	0.0699		
100	1a-2-9	0.0577		
101	1a-2-10	0.023		
102	1a-2-11	0.0475		
103	1a-2-12	0.0981		
104	1a-2-13	3.28		
105	1a-2-14	2.98		
106	1a-2-15	0.133		
107	1a-2-16	0.325		
109	1a-2-18	1.19		
110	1a-2-19	0.203		
111	1a-2-20	3.41		
112	1a-2-21	3.74		

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(continued)

Example No.	Compound No.	IC <sub>50</sub> (μM)	Compound No.	IC <sub>50</sub> (μM)
114	1a-2-23	0.929		
* reference compounds not included in the present invention				

Table 50

Example No.	Compound No.	IC <sub>50</sub> (μM)
115*	1a-2-24	0.161
117*	1a-2-26	1.19
118*	1a-2-27	0.088
119	1a-2-28	1.11
120	1a-2-29	1.53
121	1a-2-30	0.0736
122	1a-2-31	0.224
123	1a-2-32	0.0234
124	1a-2-33	0.0218
125	1a-2-34	0.0144
126	1a-2-35	0.156
127	1a-2-36	0.0243
128	1a-2-37	0.0922
129	1a-2-38	0.222
160*	1a-3-2	0.040
161*	1a-3-3	0.0108
162*	1a-3-4	0.873
163*	1a-3-5	0.0126
164*	1a-3-6	0.0965
165*	1a-3-7	0.230
166*	1a-3-8	1.28
167*	1a-3-9	0.014
168*	1a-3-10	0.0083
169*	1a-3-11	0.244
170*	1a-3-12	2.03
171*	1a-3-13	0.0395
* reference compound not included in the present invention		

Table 51\*

Example No.	Compound No.	IC <sub>50</sub> (μM)
177	1a-4-2	0.684

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(continued)

Example No.	Compound No.	IC <sub>50</sub> (μM)
178	1a-4-3	0.0252
179	1a-4-4	2.36
180	1a-4-5	0.045
181	1a-4-6	0.0539
182	1a-4-7	0.0059
183	1a-4-8	0.0027
184	1a-4-9	0.00325
185	1a-4-10	0.0422
186	1a-4-11	0.0982
187	1a-4-12	0.177
188	1a-4-13	0.843
189	1a-4-14	0.0375
190	1a-4-15	0.0597
191	1a-4-16	0.0095
192	1a-4-17	0.324
193	1a-4-18	0.722
195	1a-4-20	1.1
196	1a-4-21	0.0573
197	1a-4-22	0.0161
198	1a-4-23	0.493
199	1a-4-24	2.06
200	1a-4-25	0.173
201	1a-4-26	0.252
202	1a-4-27	0.0114
203	1a-4-28	0.173
* reference compounds, not included in the present invention		

Table 52\*

Example No.	Compound No.	IC <sub>50</sub> (μM)	Compound No.	IC <sub>50</sub> (μM)
204	1a-4-29	3.95		
207	1a-4-30	4.44		
210	1a-5-2	0.024		
211	1a-5-3	0.210	1b-211	0.00565
212	1a-5-4	0.393		
213	1a-5-5	0.128		
214	1a-5-6	0.832		
215	1a-5-7	0.110		

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(continued)

Example No.	Compound No.	IC <sub>50</sub> (μM)	Compound No.	IC <sub>50</sub> (μM)
216	1a-5-8	0.107		
218	1a-5-10	0.744		
219	1a-5-11	0.574		
220	1a-5-12	0.0167		
221	1a-5-13	0.316		
222	1a-5-14	0.078		
223	1a-5-15	0.349		
224	1a-1-16	0.0101		
225	1a-5-17	0.0122		
226	1a-5-18	0.166		
227	1a-5-19	0.0198		
228	1a-5-20	0.106		
229	1a-5-21	0.215		
230	1a-5-22	0.281		
231	1a-5-23	0.197		
232	1a-5-24	0.144		
233	1a-5-25	0.0864		
234	1a-5-26	0.153		
* reference compounds, not included in the present invention				

Table 53\*

Example No.	Compound No.	IC <sub>50</sub> (μM)	Compound No.	IC <sub>50</sub> (μM)
235	1a-5-27	0.265		
236	1a-5-28	0.304		
237	1a-5-29	1.32		
238	1a-5-30	2.85		
239	1a-5-31	0.243		
240	1a-5-32	0.0041		
241	1a-5-33	0.0131		
242	1a-5-34	0.0239		
243	1a-5-35	0.0529		
244	1a-5-36	0.0165		
245	1a-5-37	0.0059		
246	1a-5-38	0.0108		
247	1a-5-39	0.0035		
267	1a-2-66	1.5	1b-2-66	0.011
* reference compounds, not included in the present invention				

Table 54\*

Example No.	Compound No.	IC <sub>50</sub> (μM)
252	1-252	0.24
253	1-253	0.000039
254	1-254	0.00063
255	1-255	0.529
256	1-256	0.601
257	1-257	0.776
258	1-258	0.908
259	1-259	0.130
260	1-260	0.159
261	1-260	0.182
* reference compounds, not included in the present invention		

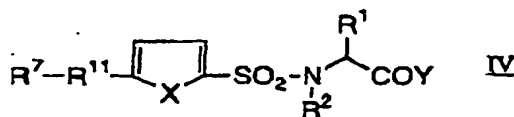
[0111] The compound of the present invention showed strong activity for inhibiting type IV collagenase.

#### Industrial Applicability

[0112] It is considered that the compound of the present invention is useful to prevent or treat osteoarthritis, rheumatoid arthritis, corneal ulceration, periodontal disease, metastasis and invasion of tumor, advanced virus infection (e.g., HIV), arteriosclerosis obliterans, arteriosclerotic aneurysm, atherosclerosis, restenosis, sepsis, septic shock, coronary thrombosis, aberrant angiogenesis, scleritis, multiple sclerosis, open angle glaucoma, retinopathies, proliferative retinopathy, neovascular glaucoma, pterygium, keratitis, epidermolysis bullosa, psoriasis, diabetes, nephritis, neurodegenerative disease, gingivitis, tumor growth, tumor angiogenesis, ocular tumor, angiofibroma, hemangioma, fever, hemorrhage, coagulation, cachexia, anorexia, acute infection, shock, autoimmune disease, malaria, Crohn disease, meningitis, and gastric ulcer, because the compound of the present invention has strong inhibitory activity against metalloproteinase, especially MMP.

#### Claims

1. A compound of the formula IV:



wherein R<sup>1</sup> is

optionally substituted C1-C6 straight or branched alkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, amino, methylamino, dimethylamino, carbamoylamino, guanidino, phenyl, or benzyloxy, optionally substituted aryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido, optionally substituted aralkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, ben-

zylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

optionally substituted heteroaryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

or

optionally substituted heteroarylalkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido;

R<sup>2</sup> is

hydrogen atom,

optionally substituted C1-C6 straight or branched alkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, amino, methylamino, dimethylamino, carbamoylamino, guanidino, phenyl, or benzyloxy,

optionally substituted aryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

optionally substituted aralkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

optionally substituted heteroaryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

or

optionally substituted heteroarylalkyl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido;

R<sup>7</sup> is

optionally substituted aryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido,

or

optionally substituted heteroaryl, wherein the substituents are hydroxy, alkoxy, mercapto, alkylthio, cycloalkyl, halogen, carboxy, alkoxycarbonyl, nitro, cyano, haloalkyl, aryloxy, amino, methylamino, dimethylamino, diethylamino, benzylideneamino, guanidino, alkyl, alkenyl, alkynyl, alkanoyl, acyloxy, acylamino, alkylsulfonyl, phenyl, benzyl, phenylazo, heteroaryl, ureido or phenylureido;

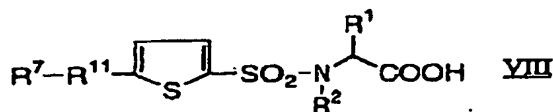
R<sup>11</sup> is -CH=CH-, or -C≡C-;

X is oxygen atom or sulfur atom;

Y is -NHOH or -OH,

its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

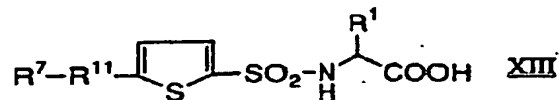
2. A compound as claimed in claim 1 represented by the formula VIII:



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>7</sup>, and R<sup>11</sup> are as defined in claim 1. its optically active substance, their pharmaceutically acceptable

salt, or hydrate thereof.

3. A compound as claimed in claim 2 represented by the formula XIII:

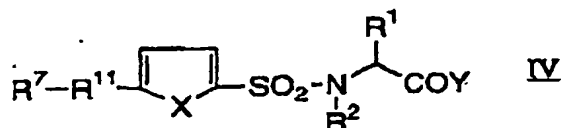


wherein R<sup>1</sup>, R<sup>7</sup>, and R<sup>11</sup> are as defined in claim 1, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

4. The compound of any one of claims 1 to 3, wherein R<sup>1</sup> is i-propyl, benzyl, or (indole-3-yl)methyl.
5. The compound of any one of claims 1 to 3, wherein R<sup>7</sup> is phenyl optionally substituted with one or more substituents selected from the group consisting of alkoxy, alkylthio, and alkyl.
6. The compound of any one of claims 1 to 3, wherein a configuration of asymmetric carbon atoms bonding with R<sup>1</sup> is R configuration.
7. A pharmaceutical composition containing a compound of any one of claims 1 to 6.
8. A composition for inhibiting metalloproteinase containing a compound of any one of claims 1 to 6.
9. A composition for inhibiting type IV collagenase containing a compound of any one of claims 1 to 6.

#### Patentansprüche

1. Verbindung der Formel IV:



wobei R<sup>1</sup> Folgendes ist

gegebenenfalls substituiertes, geradkettiges oder verzweigtes C1-C6-Alkyl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Amino, Methylamino, Dimethylamino, Carbamoylamino, Guanidino, Phenyl oder Benzyloxy sind,

gegebenenfalls substituiertes Aryl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Aryloxy, Amino, Methylamino, Dimethylamino, Diethylamino, Benzylidenamino, Guanidino, Alkyl, Alkenyl, Alkynyl, Alkanoyl, Acyloxy, Acylamino, Alkylsulfonyl, Phenyl, Benzyl, Phenylazo, Heteroaryl, Ureido oder Phenylureido sind,

gegebenenfalls substituiertes Aralkyl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Aryloxy, Amino, Methylamino, Dimethylamino, Diethylamino, Benzylidenamino, Guanidino, Alkyl, Alkenyl, Alkynyl, Alkanoyl, Acyloxy, Acylamino, Alkylsulfonyl, Phenyl, Benzyl, Phenylazo, Heteroaryl, Ureido oder Phenylureido sind,

gegebenenfalls substituiertes Heteroaryl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Aryloxy, Amino, Methylamino, Dimethylamino, Diethylamino, Benzylidenamino, Guanidino, Alkyl, Alkenyl, Alkynyl, Alkanoyl, Acyloxy, Acylamino, Alkylsulfonyl, Phenyl, Benzyl, Phenylazo, Heteroaryl, Ureido oder Phenylureido sind, oder

gegebenenfalls substituiertes Heteroarylalkyl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Aryloxy, Amino, Methylamino, Dimethyl-

amino, Diethylamino, Benzylidenamino, Guanidino, Alkyl, Alkenyl, Alkynyl, Alkanoyl, Acyloxy, Acylamino, Alkylsulfonfyl, Phenyl, Benzyl, Phenylazo, Heteroaryl, Ureido oder Phenylureido sind;

R<sup>2</sup> Folgendes ist

ein Wasserstoffatom,

gegebenenfalls substituiertes, geradkettiges oder verzweigtes C1-C6-Alkyl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Amino, Methylamino, Dimethylamino, Carbamoylamino, Guanidino, Phenyl oder Benzyloxy sind,

gegebenenfalls substituiertes Aryl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Aryloxy, Amino, Methylamino, Dimethylamino, Diethylamino, Benzylidenamino, Guanidino, Alkyl, Alkenyl, Alkynyl, Alkanoyl, Acyloxy, Acylamino, Alkylsulfonfyl, Phenyl, Benzyl, Phenylazo, Heteroaryl, Ureido oder Phenylureido sind,

gegebenenfalls substituiertes Aralkyl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Aryloxy, Amino, Methylamino, Dimethylamino, Diethylamino, Benzylidenamino, Guanidino, Alkyl, Alkenyl, Alkynyl, Alkanoyl, Acyloxy, Acylamino, Alkylsulfonfyl, Phenyl, Benzyl, Phenylazo, Heteroaryl, Ureido oder Phenylureido sind,

gegebenenfalls substituiertes Heteroaryl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Aryloxy, Amino, Methylamino, Dimethylamino, Diethylamino, Benzylidenamino, Guanidino, Alkyl, Alkenyl, Alkynyl, Alkanoyl, Acyloxy, Acylamino, Alkylsulfonfyl, Phenyl, Benzyl, Phenylazo, Heteroaryl, Ureido oder Phenylureido sind,

oder

gegebenenfalls substituiertes Heteroarylalkyl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Aryloxy, Amino, Methylamino, Dimethylamino, Diethylamino, Benzylidenamino, Guanidino, Alkyl, Alkenyl, Alkynyl, Alkanoyl, Acyloxy, Acylamino, Alkylsulfonfyl, Phenyl, Benzyl, Phenylazo, Heteroaryl, Ureido oder Phenylureido sind;

R<sup>7</sup> Folgendes ist

gegebenenfalls substituiertes Aryl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Aryloxy, Amino, Methylamino, Dimethylamino, Diethylamino, Benzylidenamino, Guanidino, Alkyl, Alkenyl, Alkynyl, Alkanoyl, Acyloxy, Acylamino, Alkylsulfonfyl, Phenyl, Benzyl, Phenylazo, Heteroaryl, Ureido oder Phenylureido sind,

oder

gegebenenfalls substituiertes Heteroaryl, wobei die Substituenten Hydroxy, Alkoxy, Mercapto, Alkylthio, Cycloalkyl, Halogen, Carboxy, Alkoxycarbonyl, Nitro, Cyano, Halogenalkyl, Aryloxy, Amino, Methylamino, Dimethylamino, Diethylamino, Benzylidenamino, Guanidino, Alkyl, Alkenyl, Alkynyl, Alkanoyl, Acyloxy, Acylamino, Alkylsulfonfyl, Phenyl, Benzyl, Phenylazo, Heteroaryl, Ureido oder Phenylureido sind;

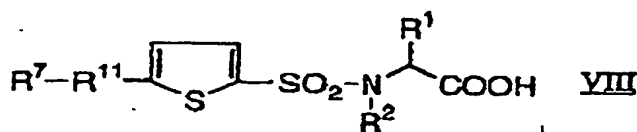
R<sup>11</sup> -CH=CH- oder -C=C- ist;

X ein Sauerstoffatom oder Schwefelatom ist;

Y -NHOH oder -OH ist;

ihre optisch aktive Substanz, deren pharmazeutisch verträgliches Salz oder deren Hydrat.

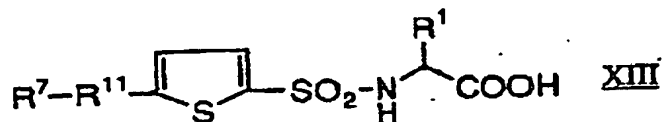
2. Verbindung nach Anspruch 1, dargestellt durch die Formel VIII:



wobei R<sup>1</sup>, R<sup>2</sup>, R<sup>7</sup> und R<sup>11</sup> wie in Anspruch 1 definiert sind, ihre optisch aktive Substanz, deren pharmazeutisch verträgliches Salz oder deren Hydrat.

3. Verbindung nach Anspruch 2, dargestellt durch die Formel XIII:



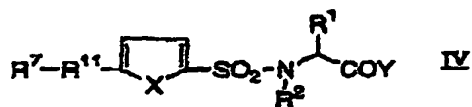


wobei R<sup>1</sup>, R<sup>7</sup> und R<sup>11</sup> wie in Anspruch 1 definiert sind, ihre optisch aktive Substanz, deren pharmazeutisch verträgliches Salz oder deren Hydrat.

4. Verbindung nach einem der Ansprüche 1 bis 3, wobei R<sup>1</sup> i-Propyl, Benzyl oder (Indol-3-yl)methyl ist.
5. Verbindung nach einem der Ansprüche 1 bis 3, wobei R<sup>7</sup> Phenyl ist, das gegebenenfalls mit einem oder mehreren Substituenten, ausgewählt aus Alkoxy, Alkylthio und Alkyl, substituiert ist.
6. Verbindung nach einem der Ansprüche 1 bis 3, wobei eine Anordnung asymmetrischer Kohlenstoffatome, die an R<sup>1</sup> gebunden sind, eine R-Konfiguration ist.
7. Arzneimittel, welches eine Verbindung nach einem der Ansprüche 1 bis 6 enthält.
8. Zusammensetzung zur Hemmung der Metalloproteinase, welche eine Verbindung nach einem der Ansprüche 1 bis 6 enthält.
9. Zusammensetzung zur Hemmung der Kollagenase vom Typ IV, welche eine Verbindung nach einem der Ansprüche 1 bis 6 enthält.

#### Revendications

1. Composé de la formule IV :



dans lequel R<sup>1</sup> est

un alkyle linéaire ou ramifié, en C1-C6, le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, amino, méthylamino, diméthylamino, carbamoylamino, guanidino, phényle ou benzyloxy,

un aryle le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, aryloxy, amino, méthylamino, diméthylamino, diéthylamino, benzylidèneamino, guanidino, alkyle, alcényle, alcynyle, alcanoyale, acyloxy, acylamino, alkylsulfonyle, phényle, benzyle, phénylazo, hétéroaryle, uréido ou phényluréido,

un aralkyle le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, aryloxy, amino, méthylamino, diméthylamino, diéthylamino, benzylidèneamino, guanidino, alkyle, alcényle, alcynyle, alcanoyale, acyloxy, acylamino, alkylsulfonyle, phényle, benzyle, phénylazo, hétéroaryle, uréido ou phényluréido,

un hétéroaryle le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, aryloxy, amino, méthylamino, diméthylamino, diéthylamino, benzylidèneamino, guanidino, alkyle, alcényle, alcynyle, alcanoyale, acyloxy, acylamino, alkylsulfonyle, phényle, benzyle, phénylazo, hétéroaryle, uréido ou phényluréido,

ou

un hétéroarylalkyle le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, aryloxy, amino, méthylamino, diméthylamino,

diéthylamino, benzylidèneamino, guanidino, alkyle, alcényle, alcynyle, alcanoyle, acyloxy, acylamino, alkylsulfonyle, phényle, benzyle, phénylazo, hétéroaryle, uréido ou phényluréido ;

R<sup>2</sup> est

un atome d'hydrogène,

un alkyle linéaire ou ramifié, en C1-C6, le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, amino, méthylamino, diméthylamino, carbamoylamino, guanidino, phényle ou benzyloxy,

un aryle le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, aryloxy, amino, méthylamino, diméthylamino, diéthylamino, benzylidèneamino, guanidino, alkyle, alcényle, alcynyle, alcanoyle, acyloxy, acylamino, alkylsulfonyle, phényle, benzyle, phénylazo, hétéroaryle, uréido ou phényluréido,

un aralkyle le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, aryloxy, amino, méthylamino, diméthylamino, diéthylamino, benzylidèneamino, guanidino, alkyle, alcényle, alcynyle, alcanoyle, acyloxy, acylamino, alkylsulfonyle, phényle, benzyle, phénylazo, hétéroaryle, uréido ou phényluréido,

un hétéroaryle le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, aryloxy, amino, méthylamino, diméthylamino, diéthylamino, benzylidèneamino, guanidino, alkyle, alcényle, alcynyle, alcanoyle, acyloxy, acylamino, alkylsulfonyle, phényle, benzyle, phénylazo, hétéroaryle, uréido ou phényluréido,

ou

un hétéroarylalkyle le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, aryloxy, amino, méthylamino, diméthylamino, diéthylamino, benzylidèneamino, guanidino, alkyle, alcényle, alcynyle, alcanoyle, acyloxy, acylamino, alkylsulfonyle, phényle, benzyle, phénylazo, hétéroaryle, uréido ou phényluréido ;

R<sup>7</sup> est

un aryle le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, aryloxy, amino, méthylamino, diméthylamino, diéthylamino, benzylidèneamino, guanidino, alkyle, alcényle, alcynyle, alcanoyle, acyloxy, acylamino, alkylsulfonyle, phényle, benzyle, phénylazo, hétéroaryle, uréido ou phényluréido,

ou

un hétéroaryle le cas échéant substitué, où les substituants sont hydroxy, alcoxy, mercapto, alkylthio, cycloalkyle, halogène, carboxy, alcoxycarbonyle, nitro, cyano, haloalkyle, aryloxy, amino, méthylamino, diméthylamino, diéthylamino, benzylidèneamino, guanidino, alkyle, alcényle, alcynyle, alcanoyle, acyloxy, acylamino, alkylsulfonyle, phényle, benzyle, phénylazo, hétéroaryle, uréido ou phényluréido ;

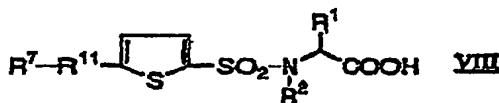
R<sup>11</sup> est CH=CH ou C≡C ;

X est un atome d'oxygène ou un atome de soufre ;

Y est NHOH ou OH,

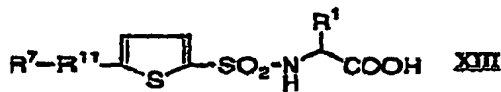
sa substance optiquement active, leur sel pharmaceutiquement acceptable ou hydrate.

2. Composé selon la revendication 1, représenté par la formule VIII :



dans laquelle R<sup>1</sup>, R<sup>2</sup>, R<sup>7</sup> et R<sup>11</sup> sont tels que définis à la revendication 1, sa substance optiquement active, leur sel pharmaceutiquement acceptable ou hydrate.

3. Composé selon la revendication 2, représenté par la formule XIII :



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dans laquelle R<sup>1</sup>, R<sup>7</sup> et R<sup>11</sup> sont tels que définis à la revendication 1, sa substance optiquement active, leur sel pharmaceutiquement acceptable ou hydrate.

4. Composé selon l'une quelconque des revendications 1 à 3, dans lequel R<sup>1</sup> est isopropyle, benzyle ou (indol-3-yl) méthyle.
5. Composé selon l'une quelconque des revendications 1 à 3, dans lequel R<sup>7</sup> est phényle le cas échéant substitué avec un ou plusieurs substituants choisis parmi le groupe consistant en alcoxy, alkylthio et alkyle.
6. Composé selon l'une quelconque des revendications 1 à 3, dans lequel la configuration des atomes de carbone asymétriques liant R<sup>1</sup> est la configuration R.
7. Composition pharmaceutique contenant un composé selon l'une quelconque des revendications 1 à 6.
8. Composition pour inhiber la métalloprotéinase, contenant un composé selon l'une quelconque des revendications 1 à 6.
9. Composition pour inhiber la collagénase de type IV, contenant un composé selon l'une quelconque des revendications 1 à 6.